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# THE LOCATION OF THE LATERAL SPINOTHALAMIC TRACT IN THE BRAIN STEM OF MAN

A. T. RASMUSSEN, PH.D., AND W. T. PEYTON, M.D., PH.D.,
MINNEAPOLIS, MINN.

*(From the Departments of Anatomy and Surgery, the Medical School, University of Minnesota)*

THE PRECISE location of the lateral spinothalamic tract is of special importance since its transection has become a recognized neurosurgical procedure for intractable pain. Only a few studies on this tract have been made on Marchi material. The superiority of the Marchi technique in defining the exact position of fibers that are scattered or mixed with others is well recognized. The latest report on this subject is by Walker,[1] who reviews the literature admirably and describes the general course of these fibers as seen primarily in a case of left chordotomy at the upper thoracic level with death eighteen days later. He furnishes further proof of the termination of the lateral spinothalamic tract in the posterolateral ventral nucleus of the thalamus.

While chordotomy is common enough, death within a few weeks after the operation under circumstances that permit the application of the Marchi technique is sufficiently rare to warrant further study of this type of material. Dogliotti[2] has successfully interrupted these fibers at the upper border of the pons. Although it would appear from his report that section of the lateral spinothalamic tract at this high level may be somewhat hazardous, and although it is also recognized that the indication is rare for severing of the fasciculus in the brain stem (in preference to a high cervical chordotomy combined with rhizotomy of the posterior roots of the upper cervical nerves), still the occasion may arise when such operative intervention would be seriously considered. To minimize the risk involved in operating at such high levels, the detailed topography of the fibers involved should be thoroughly appreciated at various points along the brain stem. We have, therefore, car-

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ried through the Swank-Davenport[3] chlorate-osmic-formalin technique blocks of tissue from every segment of the spinal cord and a complete series of blocks from the lower portion of the medulla oblongata well into the thalamus. The Swank-Davenport method blackens the fat droplets resulting from degeneration of the myelin sheath with less tendency to produce disturbing artifacts than with the conventional Marchi procedure. It also gives evidence of degeneration earlier than can be recognized by the usual Marchi technique (Swank[4]). Its utilization in neuropathology is strongly recommended.

## MATERIAL AND METHOD

The tissue was obtained from a man 54 years of age who succumbed nineteen days after right chordotomy done in the fourth to fifth thoracic segment for the relief of pain due to a metastatic squamous-cell carcinoma invading the left lumbosacral nerve plexus. Fifty-two days before death (thirty-three days prior to the chordotomy) 1 c.c. of 95 per cent alcohol had been injected through the second lumbar interspace into the subarachnoid space, according to the method of Dogliotti,[5] with the patient lying on the right side. The relief from pain was so incomplete that anterolateral chordotomy was later performed by a dorsolateral exposure and a certain amount of rotation of the cord. After the chordotomy the loss of pain and temperature sensibility extended up to the sixth thoracic dermatome on the left side. Subjectively he was entirely relieved of pain.

The brain and spinal cord were removed eight and one-half hours after death. The brain was perfused through the arteries with 3,000 c.c. of a 5 per cent equeous solution of magnesium sulfate containing 2.5 per cent potassium dichromate and left overnight in this reagent. After further fixation for a day in 10 per cent formalin, transverse blocks nearly 1 cm. thick were made of the brain stem and kept two days in 10 per cent formalin. The spinal cord was cut into its thirty-one segments (leaving a little pia on one side to act as a hinge and to keep the segments in proper sequence) and kept overnight in a liter of above magnesium-potassium sulfate and then two days in 10 per cent formalin. By coiling the spinal cord in a large round dish so that the cuts gapped, the fixer had intimate contact with the cut surfaces of all the blocks.

From each segment of the spinal cord 3 mm.-thick blocks next to the cut surface were taken and the entire brain stem cut into blocks of about this thickness. Blocks through the upper third of the midbrain and thalamus were made oblique, as shown in Fig. 21, in order to facilitate the following of the fibers as they scatter out near their termination.

These thin blocks (thirty from the spinal cord and twenty-five from the brain stem) were strung on a thread in easily identifiable groups

(with enough slack between blocks to permit them to lie flat) and kept ten days in twenty times their volume of an aqueous solution containing 0.6 per cent potassium chlorate, 0.2 per cent osmic acid, 1 per cent acetic acid, and 12 per cent formalin. After being washed in running water for twenty-four hours, the blocks were transferred directly to dioxan for three days (the solution changed daily) and infiltrated and embedded in 50° C. paraffin in flat-bottomed tins as previously described (Rasmussen[6]). Under proper temperature these soft paraffin blocks cut well at 50$\mu$ and may be mounted on slides, without albumin fixative, by dissolving away the paraffin by means of xylol applied with a medicine dropper and allowing the excess xylol to evaporate until sections are flat but have not changed color. When drying has gone too far, the sections take on a lighter hue. Since the blackened fat retains its sharp contrast better without cover glass, sections may be covered with clarite (a substitute for balsam), which on drying forms a hard protective covering. Most of the well-impregnated sections were covered with clarite and cover glass. In general the amount of osmic acid was insufficient to penetrate completely the blocks so that only sections near the cut surfaces were reliable.

The substitution of dioxan and paraffin embedding for the usual alcoholic dehydration and celloidin embedding decreases the time element considerably.

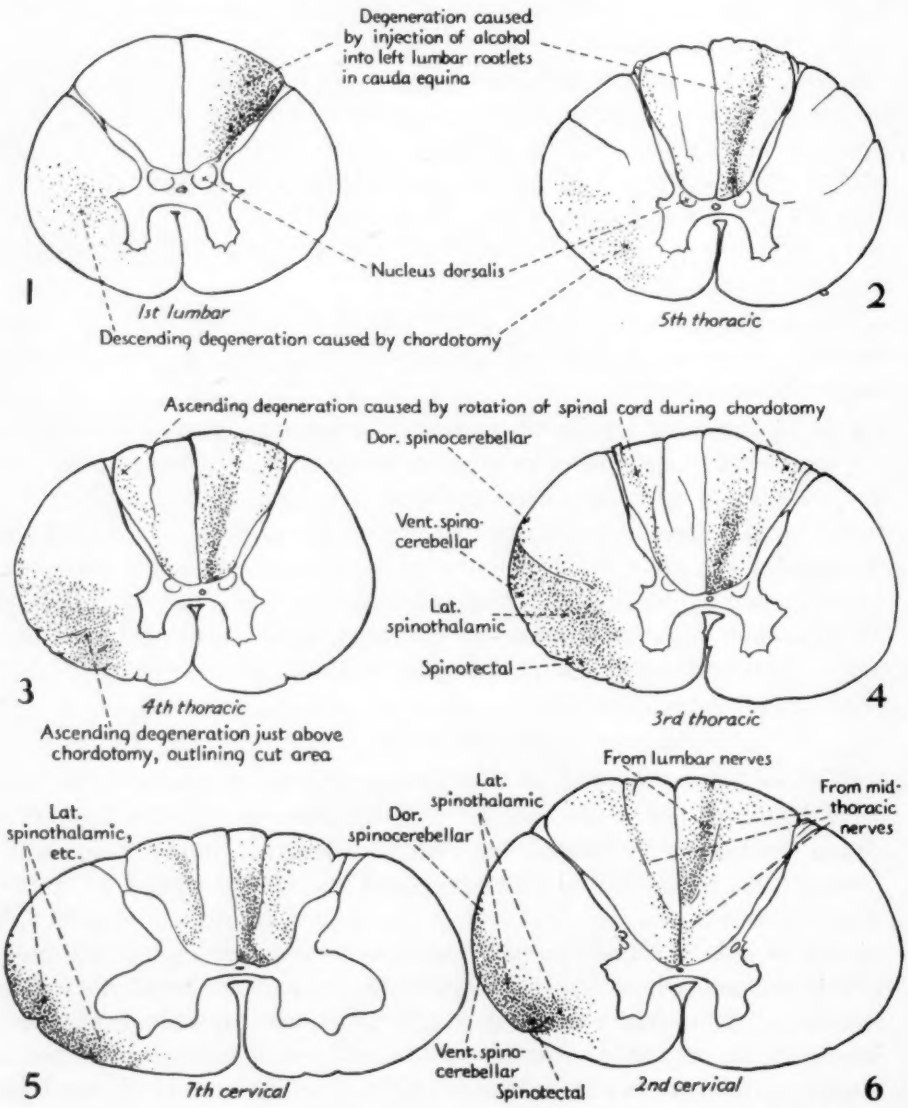
Due to the difficulty in adequately showing the detailed location of the degeneration by photomicrographs, instructive levels were projected at a known magnification (varying from six to eight times the diameter) and the visible degeneration inserted. With the original slide under the microscope the finer distribution of the degenerated fibers was carefully inserted under a higher magnification. Every effort has been made to show faithfully the relative density of the blackened fat droplets. This procedure has the advantage of a clear background, free from disturbing artifacts.

## RESULTS

Sections below the level of the incision show consistently some scattered degeneration in the ventral half of the right lateral funiculus, which diminishes in amount and shifts somewhat dorsally in lower levels. This is illustrated in Figs. 1 and 2. (In these and all subsequent cross sections the right side of the patient is on the left-hand side of the sketch.) This evidently represents descending reticulospinal fibers with possibly a few rubrospinal fibers, mostly dorsally. In the left dorsal funiculus, commencing with the lower lumbar segment and increasing in amount to the upper lumbar level, is considerable degeneration which represents the dorsal root fibers that were alcoholized one month before chordotomy was performed. From the degeneration found in different levels from the lower thoracic to the lower sacral region, it is clear that effect of the alcohol was confined to the region of the left

lumbar roots. This degeneration, as it shifts its relative position at higher levels, marks rather sharply the lumbar component of the dorsal column. Its association with nucleus gracillis is shown in Figs. 8 and 9.

In the region of the operative site, additional degeneration appears bilaterally in the lateral portion of the dorsal funiculi. This is somewhat more extensive on the right side than on the left. It is evidently due to operative exposure and traumatization of neighboring dorsal roots during rotation of spinal cord, in spite of exercising care during traction on the dentate ligament. This degeneration from trauma is




Figs. 1-6.—Various levels of spinal cord showing degeneration in dorsal funiculi resulting from injection of alcohol into lumbar roots and trauma of dorsal roots incident to exposure and rotation of spinal cord during chordotomy in fourth or fifth thoracic segment. Ascending tracts interrupted by chordotomy are shown in Fig. 4 and higher levels. (×4.)

shown in Fig. 3, which is just above the incision. Immediately above the lesion the area transected is well delimited by the degeneration and extends over most of the ventral half of the lateral funiculus. The superficial degeneration extending dorsally from the main area may be due to traumatization of the surface of the cord just dorsal to the point of entrance of the knife. This is in the region of the attachment of the dentate ligament, traction on which was used to rotate the cord.

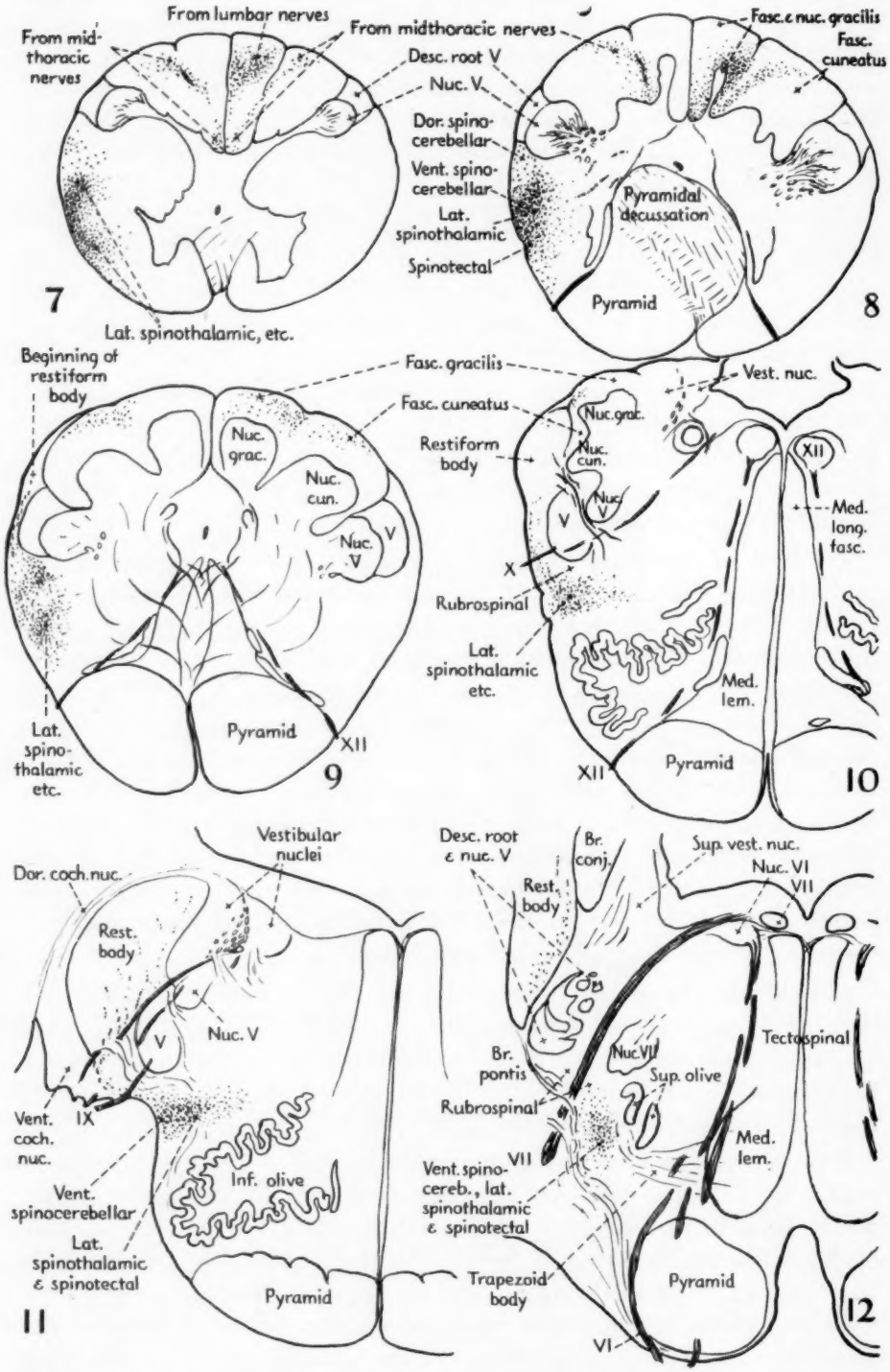
At higher levels (Figs. 5 and 6) there is confirmation of the conclusions arrived at by Hyndman and van Epps[7] with reference to the extent of the lateral spinothalamic tract. These ascending fibers cover a much larger cross section area and spread out more ventromedially than is shown in standard texts.

The extent of the involvement of the dorsal spinocerebellar tract of Flechsig is best defined in Figs. 7 to 12, which show them finally entering the restiform body. Their course within the cerebellum, curving dorsally, medially, and downward, and fanning out in the vermis, is readily seen in the material but not reproduced.

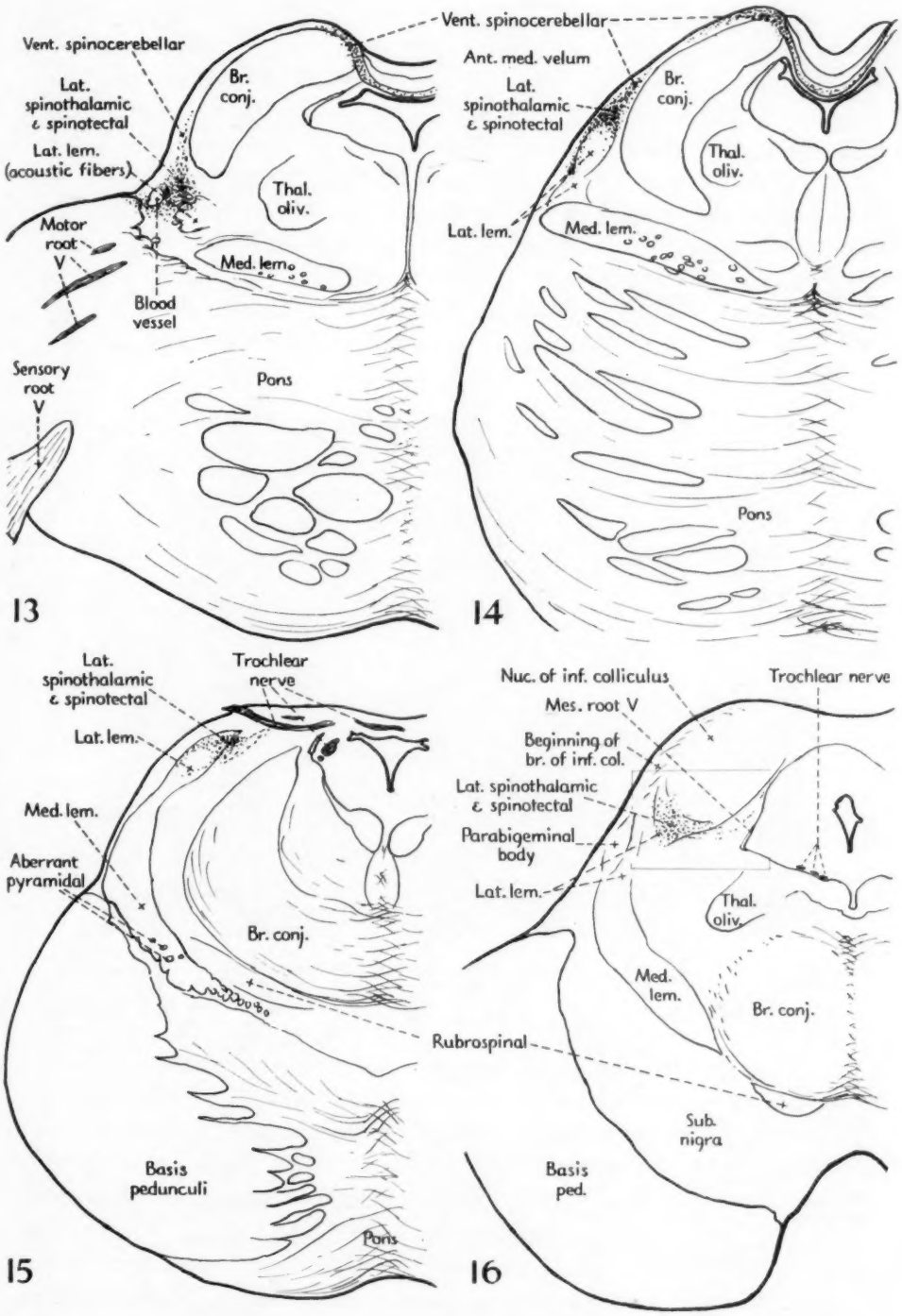
The rest of the degeneration in the lateral column consists of the ventral spinocerebellar tract of Gowers (most lateral and superficial), the small spinotectal tract (most ventrolateral), and the lateral spinothalamic tract, which constitutes the more medial and greater bulk of the degeneration. These tracts are shown in Figs. 7 to 11 in their typical position through the medulla oblongata. Near the lower pole of the inferior olive (Fig. 10) these fibers extend medially to about one-third of the distance to the midsagittal plane or about 4 mm. in the actual brain stem. Higher in the medulla (Fig. 11) they extend somewhat more medially, to a depth that makes their complete surgical interruption in this region hazardous, although the approach would be the same as for section of the descending root of the trigeminal nerve, as practiced by Sjöqvist[8] and others.[9]

Through the pons the three tracts are deeply buried. In Fig. 12 they are seen between the superior olivary nucleus and the distal part of the intrapontine portion of the facial nerve. In the upper pons they again become superficial as is illustrated in Fig. 13. Here is where Dogliotti interrupted the pain circuit.

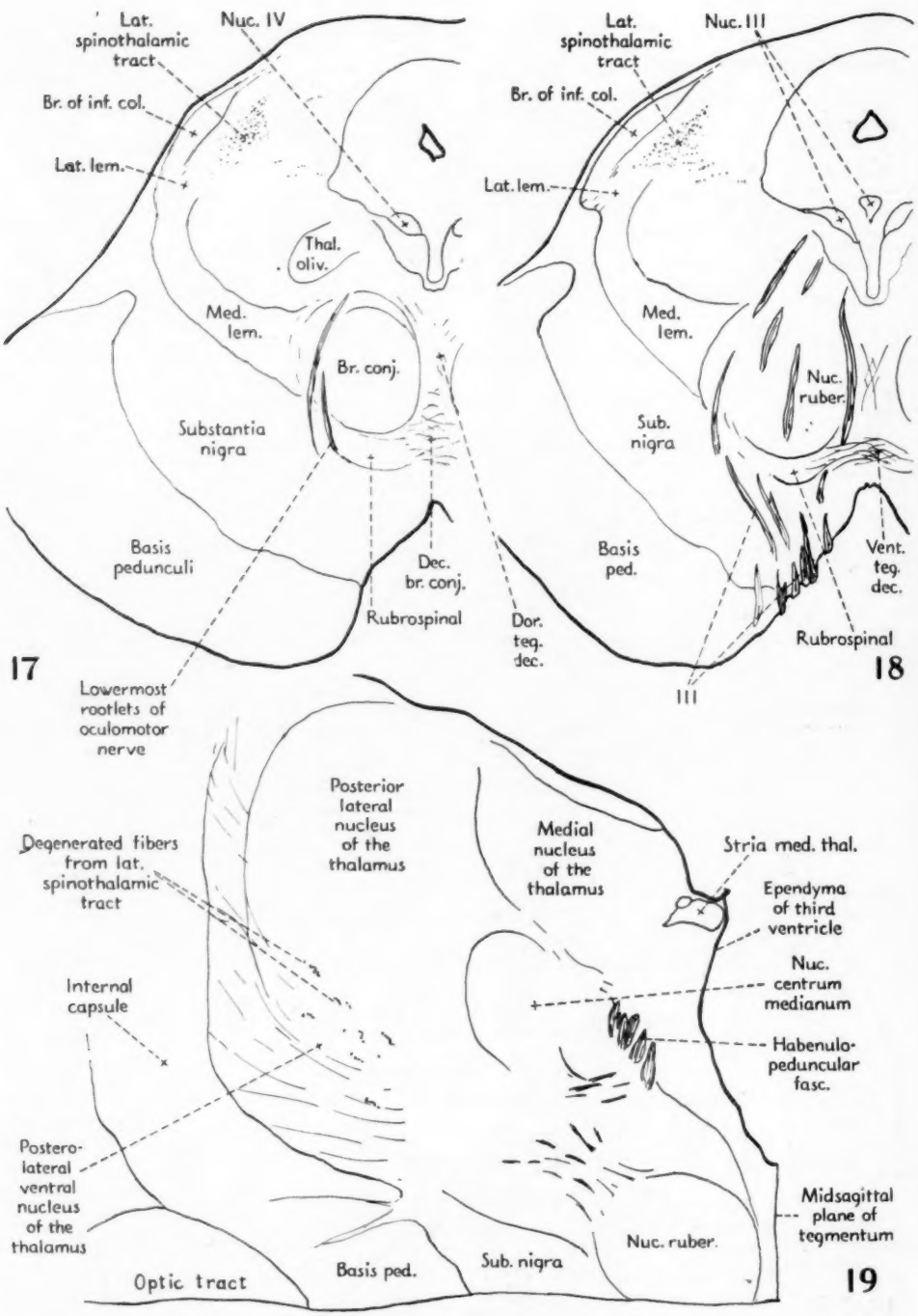
It would appear that a slightly higher level, as in Fig. 14 (compare with Fig. 21), i.e., not over 5 mm. below the fourth cranial nerve, would be a better place to cut the tract. Here (in the widest part of the trigonum lemnisci) it is spread out in a very superficial sheet less than 2 mm. in thickness, so that a shallow incision not over 2 mm. deep and about 5 mm. transversely across the central portion of the trigonum lemnisci should suffice. Some damage to the underlying superior cerebellar peduncle (brachium conjunctivum) would not be serious. Neither would ventral prolongation of the incision be of any consequence, because this would merely get more of the central acoustic




Figs. 7-12.—Various levels of medulla oblongata showing degeneration as in preceding ($\times 3\frac{1}{2}$).




Figs. 13-16.—Upper pons and lower midbrain showing particularly superficial position of lateral spinothalamic tract (×3).




Figs. 17-18.—Intercollicular region of midbrain showing lateral spinothalamic tract more deeply situated. Note spinotectal fibers (×3).

Fig. 19.—Oblique section (see Fig. 21) through posterior region of thalamus showing few fibers of lateral spinothalamic tract (×3).

fibers of the lateral lemniscus, and each ear is bilaterally represented in this pathway. Dorsal prolongation would only involve the already degenerated ventral spinocerebellar tract and the dorsal portion of the brachium conjunctivum.

At the level of emergence of the trochlear nerve (Fig. 15) the dorsal spinocerebellar tract is no longer present (having turned dorsally and downward into the anterior medullary velum), and the remaining degeneration (now representing only the lateral spinothalamic and spinotectal tracts) is more dorsal in position with reference to the trigonum lemnisci. Here the brachium conjunctivum is less likely to be encountered since it is shifting ventrally. A stab wound 3 mm. deep, commencing at the attachment of the fourth nerve and extending ventrally 3 or 4 mm., should be ample to interrupt pain completely.

Fig. 20.—Photomicrograph of region squared in Fig. 16. Shows the close relation of the lateral spinothalamic tract to the nucleus of inferior colliculus. *L*, Lateral surface of midbrain; *M*, mesencephalic root of trigeminal nerve; *IC*, nucleus of inferior colliculus. (×15.)

A certain allowance must be made for fibers from the upper regions of the spinal cord since these were not cut in this case. The total bulk of pain fibers from the entire spinal cord is therefore greater than shown here. These additional fibers would enlarge the tract somewhat, especially medially, in comparison with the area of degeneration here shown.

While the statement is made that the lateral spinothalamic tract passes through the inferior colliculus (posterior corpus quadrigeminum), it was not appreciated that they were so intimately mixed with the heavy triangular myelinated area in contact with the ventral border of the nucleus of the inferior colliculus. This region has generally been assumed to be largely auditory fibers which were destined to terminate

within the nucleus of the inferior colliculus. But the sections through this region (Fig. 16) are sharply stained and free from artifacts so that interpretation is attended with great certainty. A sufficiently high power photomicrograph of the region blocked out in Fig. 16 is shown in Fig. 20. Spinotectal fibers are seen straying medially and dorsally into the region between the nucleus of the inferior colliculus and mesencephalic root of the trigeminal nerve. This is true of all of the section from slightly below this level well up into the superior colliculus. A 3 mm. stab wound, extending 5 or 6 mm. into the ventral part of the inferior colliculus would appear feasible. This location is distinctly

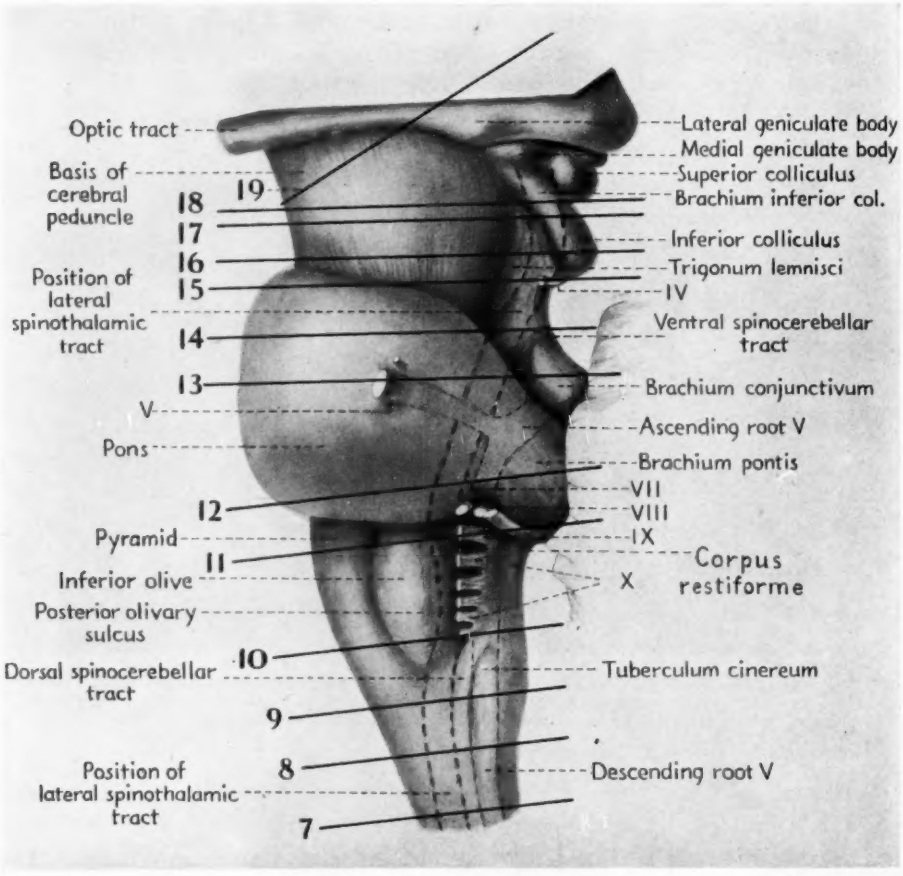



Fig. 21.—Drawing of lateral view of adult human brain stem with salient topographic features and projection of lateral spinothalamic tract and trigeminal nerve onto the surface. Numbers 7 to 19 indicate positions of cross sections shown in preceding figures with corresponding numbers. As far as location within the brain stem is concerned, the lateral spinothalamic tract is most easily accessible just below Level 15. This would appear to be a better location for interrupting it than at Level 14, where the tract has been severed. Just below Level 15 a shallow incision only 2 to 3 mm. deep and 5 to 6 mm. long transversely across the central portion of trigonum lemnisci should include the entire tract.

Tractotomy for relief of facial pain is being done at Level 10 of this figure. The descending root *V* is here covered by only a thin sheet of fibers belonging to the dorsal spinocerebellar tract. Dorsally the restiform body may slightly overlap. The lower rootlets of the vagus nerve emerge just ventral to the descending root of the trigeminal nerve. It is more probable that vagus rootlets are involved when tractotomy is followed by recurrent palsy than that the incision was too deep and damaged nucleus ambiguous, as assumed by some. (×1⅛.)

supratentorial in position and topographically easily identifiable. The nucleus of the inferior colliculus may be ignored as far as consequences following its partial destruction are concerned.

Above the inferior colliculus (Figs. 17 and 18) where the brachium of the inferior colliculus forms a prominent ridge coursing upward and slightly ventrally toward the medial geniculate body, the spinothalamic fibers are well beneath (medial to) this brachium, as noted by others.

The number of degenerated fibers that could be positively identified in the oblique sections through the lower part of the thalamus was disappointedly few. As shown in Fig. 19, only an occasional fiber could be clearly recognized and this was in the posterolateral portion of the ventral nucleus of the thalamus as maintained, especially by Walker.

The ascending degeneration, consisting mostly of the lateral spinothalamic tract, has been projected on to a side view of the brain stem (Fig. 21) in order to give a more general view of its superficial projection. The heavy transverse planes numbered from *7* to *19* represent the position of the correspondingly numbered figures. Since section of the descending (spinal) root of the trigeminal nerve is being done as a substitute for partial extrapontine section of the sensory root of this nerve, the superficial projection of this root and other portions of the fifth cranial nerve have been included in the same sketch. Careful attention has been given to the position of the descending root in the region of the lower half of the inferior olive where these fibers are most often interrupted surgically, the projection being based on about 100 gross dissections.

## SUMMARY

A description is given of the degeneration resulting from preliminary injection of alcohol into the left lumbar roots of the spinal nerves followed thirty-three days later by right chordotomy at the fourth to fifth thoracic region with death nineteen days after the chordotomy.

The usual shifting in position (in ascending levels) of the lumbar component of the dorsal funiculus (due to injection of alcohol) is well demonstrated as is also that of the fourth to fifth thoracic component (due to trauma incident to rotation of the cord).

The area of degeneration resulting from the cutting of the spinothalamic and associated tracts is larger than usually shown and thus confirms Hyndman and van Epps.

The position of the lateral spinothalamic tract through the brain stem is shown in cross sections as well as in surface projection. These fibers are most superficial in the region of the trigonum lemnisci just below the trochlear nerve, where they could readily be interrupted for relief of pain without serious consequences from direct injury to adjacent structures.

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# THE REPAIR OF A CRANIAL DEFECT WITH A VITALLIUM PLATE

W. T. Peyton, M.D., and H. B. Hall, M.D.,
Minneapolis, Minn.

*(From the Division of Neurosurgery of the Department of Surgery, the Medical School of the University of Minnesota)*

THE repair of cranial defects is a problem to the surgeon. Grant and Norcross[1] in 1939 made an exhaustive study of the literature and found more than 1,300 cases of cranioplasty described. It is unnecessary to duplicate their report, but for a complete review of cranioplastic procedures their paper should be consulted. However, some of the pertinent facts on cranioplasty bear repetition.

## HISTORICAL

Macewen in 1873 reimplanted bone into cranial defects. The bone was removed from the patient's skull, sterilized with antiseptics, and then replaced into the defect. Von Hinterstoisser[2] in 1891 was the first to describe the use of a nonosseous substance in the repair of cranial defect when he resorted to a celluloid plate. In 1893 Booth and Curtis[3] employed an aluminum plate to cover a cranial defect. Two years later Gerster[4] described the application of a gold plate. Sicard and Dambrin[5] in 1917 reported a case in which cadaver skull bone was used to repair a defect of the cranium. During the past forty years many surgeons have used both split rib grafts and cartilage to repair cranial defects. Fair success has been encountered with both rib and cartilage grafts, but most authors claim that cartilage has a little too much "give" and because of this fact it does not offer sufficiently firm support.

## VARIOUS OPERATIVE TECHNIQUES

In 1890 Müller[6] described a skull flap technique for the repair of a cranial defect. This procedure consisted in the elevation of a skin flap over the defect and then removal of an area of outer table from the adjacent bone, sliding it over to cover the defect. In the same year König[7] improved upon Müller's operation when he developed a twin flap technique. One flap consisted of skin and what remained of the pericranium over the defect, and the second flap contained skin, pericranium, and outer table. The bases of these two flaps were opposite but not directly in line with each other. The flap containing the outer table was swung over to cover the defect, while the other flap was used to cover the bared inner table. Small exposed areas produced by this crossing of flaps were covered with Thiersch grafts.

One is apparently justified in the assumption that no entirely satisfactory method has been developed for the repair of large cranial defects.

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### INDICATIONS AND CONTRAINDICATIONS

Most authors agree upon the indications and contraindications for cranioplasty which have been listed by Grant and Norcross as follows:

*Indications:*

1. Severe headache
2. Syndrome of the trephined (dizziness, apprehension and feeling of insecurity, undue fatigability, mental depression, and intolerance to vibration)
3. Epilepsy, if the attack is related to the injury
4. Danger of trauma at the site of defect
5. Unsightly defect
6. Painful defect or undue pulsation

*Contraindications:*

1. Presence of a foreign body
2. Infection of the skin, dura, or brain tissue
3. Increased intracranial pressure
4. Abnormal spinal fluid findings

### TYPES OF CRANIOPLASTIC MATERIAL

An ideal cranioplastic material should be: (1) nonirritating, both electrically and chemically; (2) strong and inelastic; (3) light weight; (4) nonabsorbable; and (5) malleable.

None of the materials used for cranioplasty have been entirely satisfactory. Either cadaver or fresh human bone may absorb or fail to unite solidly. If infection occurs, the bone graft may slough out.

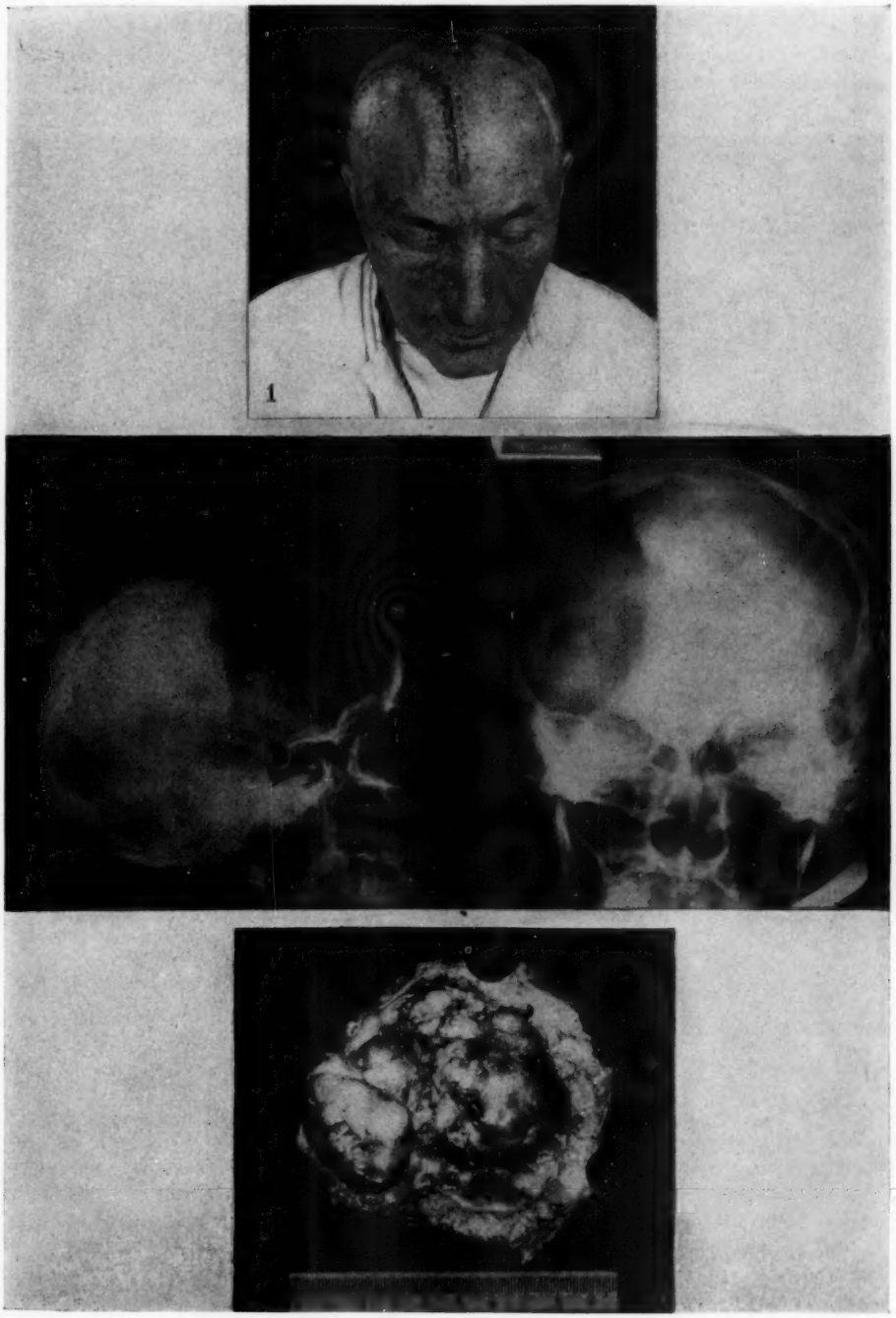
Vitallium, an alloy of chrome, cobalt, and molybdenum, was developed for the dental profession in 1929 in a search for an inactive metal. In 1936 Venable and Stuck reported their experiences with vitallium in bone surgery. They found it to be absolutely inactive when it is in contact with tissue. No changes could be detected either in the tissue or in the metal itself. It has been used in bone surgery for the past four years and has proved most satisfactory. Vitallium is not malleable, but this is chiefly a manufacturing disadvantage and not a surgical one. Malleability of the metal used, however, is desirable at times in order that a plate be molded to fit a part, but this is of minor importance among the requirements for a suitable cranioplastic substance.

### REPORT OF A CASE

The employment of vitallium by the orthopedic staff prompted us to investigate the possibility of fashioning a plate from this alloy to cover a cranial defect in the following case:

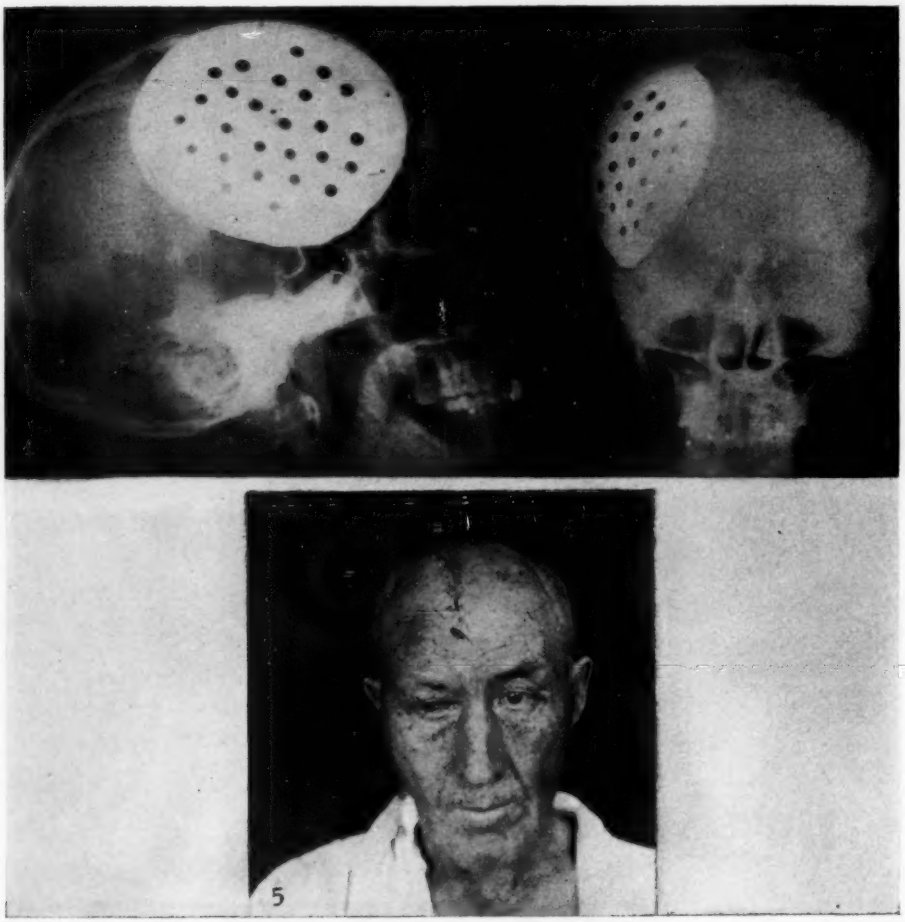
T. E. (U.H. 690902), a 61-year-old white male, was referred to the University of Minnesota Hospital Clinics for the diagnosis and treatment of a tumor mass involving the right side of the skull. The patient gave a history that the mass first appeared in March, 1939. The patient's local physician explored the tumor and removed a piece for biopsy, following which the patient received a series of deep x-ray treatments in July, 1939. The tumor continued to enlarge and in January, 1940, the patient was referred to the University of Minnesota Hospitals for further

care. His only complaints were a mass on the right side of the head and an occasional headache. Examination was negative except for the presence of a firm, nontender, fixed tumor mass about 10 cm. in diameter involving the cranium over the right frontoparietal region. Roentgenograms of the skull showed changes suggestive of a meningioma. On Feb. 7, 1940, through a right transfrontal incision a meningioma was excised, removing the involved bone and meningioma en masse. This left




Figs. 1-3.—Fig. 1, After excision of tumor mass; Fig. 2, roentgenograms to show defect in skull; Fig. 3, intracranial surface of tumor and bone.

a cranial defect 11 cm. in diameter and nearly round. Following an uneventful convalescence, the patient was dismissed on Feb. 16, 1940. Three months later the patient returned to the Out-Patient Clinic for a checkup. At that time he complained of a feeling of insecurity as he was afraid of suffering an injury at the site of the skull defect. Also great changes in temperature, such as the application of hot or cold water to the defect, were quite unpleasant. Examination at that time was negative except for the pulsating defect. The patient desired that something be done to cover the area of excised bone. As the defect was so large, it would have been nearly impossible to carry out a Müller-König procedure; therefore, this case appeared to be the type suitable for the application of a vitallium plate.




Figs. 4 and 5.—Fig. 4, Roentgenograms to show vitallium plate in place; Fig. 5, two weeks after insertion of plate.

*Construction of a Model.*—A plaster mold was made of the right side of the skull and upper part of the face. This mold acted as the negative model. With the help of the dental department, a positive model was made and in this way an exact duplication of the cranial defect was obtained. Wax was poured into the defect and molded to conform with the surrounding contour. The wax model thus became an exact replica of the excised bone. From the positive plaster mold and wax model the plate was cast.

Fixation of the plate to the skull is a problem for each individual case. One might add "ears" to the edge of the plate. Through a hole in the center of each ear,

the plate could be fixed to the skull by screws. However, after making several such models, fixation by this method did not seem adequate; also, if it were necessary to remove bone at the time of application of the plate, the plate might fail to cover the enlarged defect. With this thought in mind, other plates were devised. The plate which seemed to be most practical was one which had a 1.5 cm. edge added beyond the edge of the defect, about two-thirds of the way around its circumference on its superior, anterior, and posterior margins. This added width allowed the plate to rest against bone over this part of the circumference. Holes were placed in the extended portion of the plate 0.5 cm. from the edge and 4 cm. apart. Larger perforations were also placed throughout the plate in order to allow the development of adhesions and blood supply between the scalp and underlying tissue.

*Operative Procedure.*—The patient was readmitted to the hospital for application of the vitallium plate on June 27, 1940. The skin and scalp flap was re-elevated, exposing the operative defect. After removal of a small amount of bone, the plate covered the defect quite satisfactorily. The overlapping rim contacted the surrounding bone snugly. The overlap was sufficient to allow fixation of the plate to the skull either by screws or wire. Stainless steel wire was used in this case as the vitallium screws which had been made to order were too short. Screws for fixation should be pointed similar to the wood type of screw and they should be 3/16 to 1/4 inch long. Because the prepared screws were not suitable, two small drill holes 0.5 cm. apart were placed in the skull directly under a hole in the plate. One end of the wire was passed through one hole in the skull and then back out through the second hole and on through the hole in the plate. The other end of the wire was brought around the edge of the plate and the ends were twisted. Three sets of holes and wires gave adequate fixation. The skin flap was reapproximated without difficulty. The convalescence was smooth except for an accumulation of fluid between the skin flap and plate which necessitated aspiration five or six times. Postoperative roentgenograms of the skull showed the plate to cover the defect adequately.

Since the insertion of the plate, the patient has experienced much relief through a feeling of security against injury. Sudden changes in temperature no longer are unpleasant to him. The cosmetic result is very satisfactory.

## CONCLUSIONS

Vitallium, an alloy of chrome, cobalt, and molybdenum, is the most inactive and practical alloy yet offered to the surgeon.

A vitallium plate offers the surgeon an almost ideal material for closure of cranial defects caused by the loss of bone.

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# THE GLYCOGEN CONTENT OF THE HUMAN LIVER*

DUGALD S. MACINTYRE,† M.D., SVEND PEDERSEN, PHD., AND WALTER G. MADDOCK, M.D., ANN ARBOR, MICH.

*(From the Department of Surgery of the University of Michigan)*

IN RECENT years much attention has been focused on the value for surgical patients of a diet high in carbohydrate or protein, or high in both, particularly in relation to the level of liver glycogen in instances of hepatic disease. Unfortunately, little is known concerning the effect of diet, anesthesia, and liver pathology upon the glycogen levels of the living human liver, except by inference, as the greater part of our knowledge has been obtained either from analyses carried out on human livers at the time of autopsy or from experimental work on animals.

The purposes of this paper are: (1) briefly to review a part of the literature relative to glycogen levels of the human liver at the time of autopsy, and (2) to present and discuss the glycogen values in the human liver obtained from biopsy specimens during surgical operations.

The great French physiologist, Claude Bernard, was the first to find in animal livers a substance similar in composition to starch in the vegetable kingdom. He named it glycogen. Although follow-up studies were mainly carried out by other investigators, Bernard did show that there was a rapid postmortal change of liver glycogen into glucose. Yet, in spite of this timely warning, many subsequent workers have entirely disregarded the fact and directly determined liver glycogen twenty-four to forty-eight hours after death and have drawn conclusions from these findings in regard to the glycogen values present during life. The most unusual claim found in this connection was that of Krukow,[1] who stated that at room temperature animal and human livers require a high state of decomposition and as long as sixty-eight days to change the greater part of the glycogen into glucose.

Determinations of glycogen in the human liver at the time of autopsy have been carried out either by chemical or histologic methods, sometimes by both. Histologic determinations can at best only be semiquantitative and will not be discussed here. Several references, however, will be included in the bibliography and particular attention is called to the great amount of medicolegal work by Meixner[2, 3] relative to the level of glycogen and the cause of death. Chemical determinations of liver glycogen can arbitrarily be grouped according to the

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†Captain Dugald S. MacIntyre, Medical Corps, is now stationed at the Beaumont Hospital, El Paso, Tex.

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method employed. The first and direct method was based upon the extraction of glycogen from the liver by hot water and the subsequent weighing of the dried glycogen. Bernard used this method in part of his work. Külz, in 1876,[4] determined glycogen on a part of a diabetic liver twelve hours after death and estimated that there were 10 to 15 Gm. in the whole gland. In 1881[5] he reported 5.28 per cent in another case. Cramer, in 1888,[6] boiled the liver in strong potassium hydroxide, precipitated the glycogen with alcohol and weighed the glycogen. In the livers from 3 infants he found respectively 1, 1.2, and 2.15 per cent. Schönheimer, in 1929,[7] found 10.4 per cent in a case of von Gierke's disease, and as high as 15.3 per cent has been reported in this condition.[8] The values obtained by water extraction of glycogen of necessity must have been minimum values as one can seldom obtain the liver from cadavers until after several hours of delay and, furthermore, the extraction by hot water is long and tedious, as well as likely to be incomplete.

The second method was based upon the destruction of the liver tissue by hot potassium hydroxide. This treatment leaves glycogen intact so that it can be precipitated by alcohol, washed, dried, and weighed, or the glycogen can be subjected to acid hydrolysis yielding glucose which can be determined by (a) various oxidizing solutions or (b) the aldehyde color reaction. By the use of the first method, Rosenbaum[9] found in 19 infant livers no glycogen in 6, traces in 6, and from 0.23 to 3.27 per cent in the remainder. Geelmuyden[10] in 14 cases found values between 0.0 and 3.02 per cent. Sandmeyer[11] found 0.61 per cent and Helly[12] 0.45 per cent. Both cases died in diabetic coma. Among French investigators, Lacassagne and Martin[13] found on an average from 2 to 3 per cent in the liver of persons dying a violent death. Later[14] they claimed a variation between 2 and 4 per cent. Garnier[15] also reported 2 to 4 per cent.

The aldehyde reaction of Dische and Popper[16] was applied by Burghard[17] and by Burghard and Paffrath.[18, 19] In 100 livers they reported for healthy infants 2 to 3 per cent and 6 to 8 per cent for healthy adults. In disease much lower values were found; only about one-third were above 1 per cent with a total range between 0.2 and 5.45 per cent. These authors concluded that there was a definite and constant difference between total carbohydrate determined as glucose and the glycogen. This difference was set by them arbitrarily at 0.23 which, when subtracted from the total carbohydrate, indirectly would give glycogen present "at the time of death." This constant difference was not confirmed by Hertz,[20] who reported variations between 0.46 and 12.6 per cent in a series of 2 newborn infants and 7 fetuses.

By far the most work using the aldehyde method was by Popper and Wozasek who studied 177 human livers.[21-24] In a long article[21] they classified their findings according to the disease but, stated briefly, their

glycogen values were between 0.24 and 8.5 per cent. With a few exceptions; values were between 1.56 and 6.17 per cent in patients dying suddenly without previous disease; while in livers from patients dying after long-standing diseases the values ranged between 0.24 and 1.53 per cent. It should be pointed out, also, that there was a tendency towards lower values in hepatic diseases.

These figures for liver glycogen are levels found at the time of autopsy. They do not, therefore, represent actual values which one might expect to find in sick or healthy persons during life. It should be pointed out here that the values for liver glycogen found in our study were influenced by many factors and, also, do not necessarily represent those found in the normal living human liver. Some of our patients had morphine preoperatively and "morphine diabetes" has been known for more than sixty years. Frank and Förster[25] showed in rabbits a marked decrease in liver glycogen after morphine. The same effect upon blood sugar and liver glycogen has also been observed after the administration of certain anesthetics. Evans and his associates[26] found a 20 per cent decrease in the liver glycogen of cats killed after ten minutes of an ether anesthetic and a decrease of 50 per cent after one hour. Rhythmic changes in the level of liver glycogen were observed by Forsgren[27, 28] and confirmed by others.[29-32] There may even be more than one type of glycogen present in the liver[33] and it has been claimed that certain foods as well as specific sugars form a glycogen more stable than usual. Since our liver specimens were obtained by biopsy, it is important to know if liver glycogen is equally distributed throughout the liver. In the older literature there was disagreement in regard to this point, but more recent work[4, 34-36] indicates that the content of the different lobes is sufficiently uniform that a specimen from one lobe is indicative of the whole. Experiments by us on the rat liver also favor this view.* In addition there are the general state of nutrition of the patient and the degree and duration of liver damage as well as the effect of the hormones from the thyroid, pancreas, and adrenal glands. One factor, namely, the postmortal change of glycogen into glucose, did not influence the data to be presented. The importance of this factor is shown by the finding of 0.55 per cent and 0.05 per cent of liver glycogen, by the method later described, in 2 human autopsy livers without sign of liver damage obtained two and sixteen hours respectively after death.

## PROCEDURE

The Good, Kramer, and Somogyi[37] modification of Pflüger's classical method was used for the glycogen determinations. The biopsy specimens were frozen immediately in carbon-dioxide snow and ether in the operating room. While still solidly frozen the specimens were ground very fine and transferred into weighed centrifuge tubes containing

*Unpublished data.

potassium hydroxide, were quickly weighed and placed in a beaker of boiling water. After the specimen was in solution, the glycogen was precipitated and hydrolyzed and then the total reducing sugar was determined on aliquotes in duplicate according to the method of Shaffer and Somogyi.[38] The liver specimens, removed from the liver edge, weighed 0.5 to 1.5 Gm. Bleeding was very easily controlled by inserting a small piece of abdominal wall muscle into the liver wound and approximating the cut surfaces with silk sutures. No glucose was given parenterally during the operations. The general health of each patient was estimated as being good, fair, or poor. A small piece of the liver specimen was sent to the Department of Pathology for histologic examination and was graded normal or showing slight, moderate, or advanced damage. The time of the biopsy from the onset of the anesthetic was recorded as was also any supplementary glucose feeding within twelve hours prior to the operation. These and other pertinent data are given in Table I.

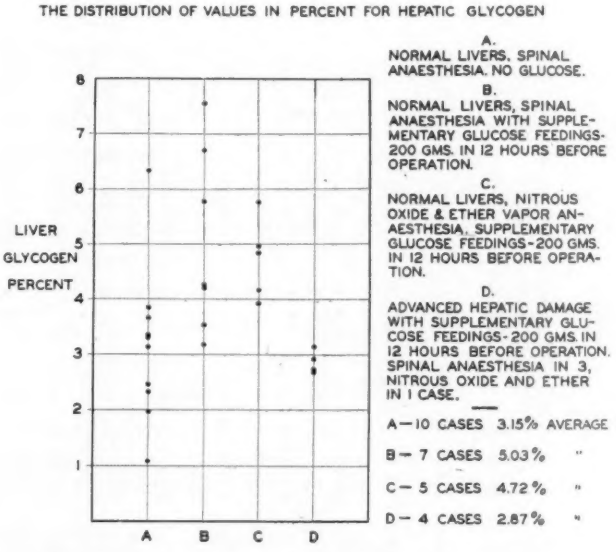
THE DISTRIBUTION OF VALUES IN PERCENT FOR HEPATIC GLYCOGEN
LIVER GLYCOGEN PERCENT
8
7
6
5
4
3
2
1
A
B
C
D
A.
NORMAL LIVERS, SPINAL ANAESTHESIA. NO GLUCOSE.
B.
NORMAL LIVERS, SPINAL ANAESTHESIA WITH SUPPLEMENTARY GLUCOSE FEEDINGS-200 GMS. IN 12 HOURS BEFORE OPERATION.
C.
NORMAL LIVERS, NITROUS OXIDE & ETHER VAPOR ANAESTHESIA, SUPPLEMENTARY GLUCOSE FEEDINGS-200 GMS. IN 12 HOURS BEFORE OPERATION.
D.
ADVANCED HEPATIC DAMAGE WITH SUPPLEMENTARY GLUCOSE FEEDINGS-200 GMS. IN 12 HOURS BEFORE OPERATION. SPINAL ANAESTHESIA IN 3, NITROUS OXIDE AND ETHER IN 1 CASE.
A—10 CASES 3.15% AVERAGE
B—7 CASES 5.03% "
C—5 CASES 4.72% "
D—4 CASES 2.87% "

Fig. 1.—Analysis of data, dividing the patients into groups according to the anesthetic, the liver pathology, and whether or not they received supplementary feedings of glucose in the twelve hours immediately preceding the operation.

## RESULTS

In the 33 cases studied and summarized in Table I, the average glycogen content was 3.96 per cent, the lowest value was 1.1 per cent, and the highest 7.56 per cent. Fig. 1 is an analysis of these data dividing the patients into groups according to the anesthetic, the liver pathology, and whether or not they received supplementary feedings of glucose in the twelve hours immediately preceding the operation. Except in those instances in which glucose was given, the patients did not receive food or fluid in the twelve hours before the operation. All cases

TABLE I

COLLECTED DATA ON 33 PATIENTS IN WHOM BIOPSIES OF THE LIVER WERE OBTAINED AND PERCENTAGE OF HEPATIC GLYCOGEN DETERMINED

| PATIENT | AGE | SEX | AVERAGE WEIGHT (KG.) | PRESENT WEIGHT (KG.) | ESTIMATE OF GENERAL HEALTH | DIAGNOSIS | DURATION OF SYMPTOMS | LIVER HISTOLOGY | ANESTHESIA | TIME FROM ONSET FOR ANESTHESIA TO BIOPSY (MIN.) | SUPPLEMENTARY GLUCOSE FEEDINGS IN 12 HR. PREOPERATIVELY (GM.) | PER CENT LIVER GLYCOGEN | POSTOPERATIVE COURSE | GROUP |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 23 | F | 67 | 60 | Fair | Cholecystitis | 4.3 mo. | Normal | Spinal | 45 | 0 | 1.10 | Fair | A |
| 2 | 27 | F | 68 | 54 | Fair | Duodenal ulcer | 24 mo. | Normal | Spinal | 39 | 0 | 1.99 | Fair | A |
| 3 | 54 | F | 64 | 46 | Poor | Duodenal obstruction | 4 mo. | Normal | Spinal | 35 | 0 | 2.32 | Death after 4 days | A |
| 4 | 58 | F | 84 | 85 | Good | Cholecystitis | 24 mo. | Normal | Spinal | 42 | 0 | 2.48 | Good | A |
| 5 | 64 | M | 72 | 59 | Fair | Gastric carcinoma | 9 mo. | Normal | Spinal | 38 | 0 | 3.12 | Good | A |
| 6 | 52 | M | 90 | 75 | Good | Cholecystitis | 36 mo. | Normal | Spinal | 60 | 0 | 3.31 | Good | A |
| 7 | 30 | F | 53 | 53 | Good | Cholecystitis | 24 mo. | Normal | Spinal | 45 | 0 | 3.34 | Good | A |
| 8 | 50 | F | 54 | 54 | Good | Cholecystitis | 6 mo. | Normal | Spinal | 40 | 0 | 3.68 | Good | A |
| 9 | 21 | F | 77 | 77 | Good | Cholecystitis | 12 mo. | Normal | Spinal | 50 | 0 | 3.85 | Good | A |
| 10 | 50 | F | 68 | 64 | Good | Cholecystitis | 12 mo. | Normal | Spinal | 39 | 0 | 6.31 | Good | A |
| 11 | 53 | M | 68 | 64 | Good | Cholecystitis | 10 yr. | Normal | Spinal | 25 | 200 | 3.19 | Fair | B |
| 12 | 58 | M | 75 | 56 | Fair | Duodenal ulcer | 20 yr. | Normal | Spinal | 38 | 200 | 3.54 | Good | B |
| 13 | 67 | F | 90 | 80 | Poor | Cholecystitis | 7 yr. | Normal | Spinal | 44 | 200 | 4.20 | Death in operating room | B |
| 14 | 53 | M | 72 | 58 | Fair | Gastric carcinoma | 4 mo. | Normal | Spinal | 32 | 200 | 4.25 | Good | B |
| 15 | 27 | F | 81 | 79 | Good | Cholecystitis | 3 mo. | Normal | Spinal | 58 | 200 | 5.79 | Good | B |
| 16 | 65 | F | 67 | 67 | Good | Cholecystitis | 12 mo. | Normal | Spinal | 35 | 200 | 6.70 | Nausea and vomiting | B |
| 17 | 54 | F | 72 | 72 | Good | Cholecystitis | 4 yr. | Normal | Spinal | 35 | 200 | 7.56 | Nausea and vomiting | B |

| | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 18 | 30 | F | 42 | 45 | Good | Cholecystitis | 3 yr. | Normal | $N_2O$ and ether | 31 | 200 | 3.91 | Good | C |
| 19 | 35 | F | 70 | 70 | Good | Cholecystitis | 13 yr. | Normal | $N_2O$ and ether | 90 | 200 | 4.17 | Fair | C |
| 20 | 55 | M | 96 | 60 | Poor | Gastric carcinoma | 7 mo. | Normal | $N_2O$ and ether | 70 | 200 | 4.82 | Good | C |
| 21 | 55 | M | 72 | 44 | Poor | Gastric carcinoma | 7 yr. | Normal | $N_2O$ and ether | 30 | 200 | 4.98 | Fair | C |
| 22 | 51 | F | 56 | 56 | Good | Cholecystitis | 3 yr. | Normal | $N_2O$ and ether | 90 | 200 | 5.75 | Good | C |
| 23 | 59 | M | 73 | 60 | Poor | Obstructive jaundice | 10 wk. | Advanced damage | Spinal | 25 | 200 | 2.70 | Good | D |
| 24 | 36 | M | 75 | 60 | Poor | Obstructive jaundice | 5 mo. | Advanced damage | Spinal | 42 | 200 | 2.74 | Death 14 days post-operatively | D |
| 25 | 65 | F | 81 | 72 | Poor | Obstructive jaundice | 5 mo. | Advanced damage | $N_2O$ and ether | 105 | 200 | 2.91 | Fair | D |
| 26 | 77 | M | 55 | 43 | Poor | Gastric carcinoma | 2 yr. | Advanced damage | Spinal | 25 | 200 | 3.14 | Poor | D |
| 27 | 60 | M | 78 | 60 | Poor | Gastric carcinoma | 9 mo. | Moderate damage | Spinal | 14 | 0 | 1.22 | Good | E |
| 28 | 69 | F | 72 | 56 | Fair | Cholecystitis | 4 yr. | Slight cirrhosis | Cyclopropane | 45 | 200 | 4.14 | Good | E |
| 29 | 63 | F | 50 | 50 | Poor | Cholecystitis | 45 days | Slight cirrhosis | Local | 30 | 200 | 4.40 | Fair | E |
| 30 | 51 | F | 46 | 34 | Poor | Duodenal ulcer | 3 mo. | Normal | $N_2O$ and ether | 18 | 0 | 4.45 | Good | E |
| 31 | 69 | F | 66 | 62 | Poor | Carcinoma of gall bladder | 8 mo. | Moderate damage | Cyclopropane, ether and $N_2O$ | 86 | 200 | 4.48 | Death 8 days post-operatively; hepato-renal syndrome | E |
| 32 | 28 | F | 45 | 45 | Good | Cholecystitis | 12 mo. | Normal | Cyclopropane | 38 | 0 | 4.65 | Good | E |
| 33 | 58 | F | 76 | 78 | Good | Hyperinsulinism | 9 yr. | Normal | Spinal | 235 | 0 | 5.56 | Good | E |

received approximately the same preoperative medication, and the biopsies were taken at approximately the same time of day.

*Percentage of Glycogen in Cases With Normal Livers.*—Group A in Fig. 1 shows the distribution of values in percentage of liver glycogen for 10 patients whose general condition with one exception was fair or good. These patients all were operated upon under spinal anesthesia, their livers were normal to both gross and microscopic examination, and none of these patients received supplementary glucose feedings. The average percentage for this good group undergoing a major operative procedure was 3.15; the range from 1.1 to 6.31 per cent.

Group B, in contrast to Group A, had conditions of general health, diagnosis, liver histology, and anesthesia similar to Group A, but in addition received supplementary feedings of glucose which were given in divided doses of 50 Gm. of glucose in 30 c.c. of lemon juice, two doses in the evening and two doses in the morning before operation. The average percentage of their liver glycogen was 5.03; the values ranged from 3.19 to 7.56. The lowest value for Group B was slightly higher than the average for the patients in Group A, who did not receive the supplementary glucose feedings. On the basis of average percentage alone, Group B showed a 60 per cent increase over Group A.

Group C consists of 5 patients who were operated upon under nitrous oxide and ether anesthesia, and whose livers were found to be normal. All of these patients received supplementary glucose feedings and their average hepatic glycogen content was 4.72 per cent, which is slightly lower than the average for similar patients operated upon under spinal anesthesia.

*Percentage of Glycogen in Cases With Liver Damage.*—The ability of a damaged liver to store glycogen is shown by Group D in Fig. 1 in which are placed 4 patients with advanced hepatic pathology. The operations were performed either under spinal or nitrous oxide and ether anesthesia. All 4 cases received 200 Gm. of glucose in the twelve hours immediately preceding the operation. Here the average percentage of hepatic glycogen for the 4 cases was 2.87, which is only about one-half the average value obtained in cases that had normal livers. This demonstrates the apparent inability of damaged livers to synthesize and store glycogen in as large amounts as the normal liver. We feel that the levels of glycogen found in these patients with damaged livers probably represent nearly maximum values, since all 4 patients were hospitalized at least five days prior to their operation and received a high carbohydrate, low fat diet during that time and in addition were given supplementary glucose feedings up to within three hours before their operation, thus tending to avoid the drop in hepatic glycogen due to fasting which is most marked in high carbohydrate fed animals.

*Changes in Liver Glycogen During Operations Under Spinal Anesthesia.*—Table II shows the variations during operation of the glycogen content of the human liver. As can be seen, with the exception of

TABLE II

CHANGES IN LIVER GLYCOGEN DURING OPERATIONS UNDER SPINAL ANESTHESIA (17 C.C. 1:1,500 NUPERCAINE)

| PATIENT NO. | PERCENTAGE GLYCOGEN | | DIFFERENCE BETWEEN GLYCOGENS | TIME BETWEEN BIOPSIES (MIN.) | SUPPLEMENTARY GLUCOSE FEEDING IN 12 HRS. PREOPERATIVELY (GM.) | DIAGNOSIS | ESTIMATE OF GENERAL HEALTH | LIVER HISTOLOGY | POSTOPERATIVE COURSE |
|---|---|---|---|---|---|---|---|---|---|
| | FIRST BIOPSY | SECOND BIOPSY | | | | | | | |
| 2 | 1.99 | 1.60 | – .39 | 68 | 0 | Duodenal ulcer | Fair | Normal | Fair |
| 3 | 2.32 | 0.96 | –1.36 | 70 | 0 | Duodenal obstruction | Poor | Normal | Death 4 days postoperatively |
| 4 | 2.48 | 3.10 | .62 | 56 | 0 | Cholecystitis | Good | Normal | Good |
| 5 | 3.12 | 3.00 | – .12 | 142 | 0 | Gastric carcinoma | Fair | Normal | Good |
| 8 | 3.68 | 3.79 | .11 | 27 | 0 | Cholecystitis | Good | Normal | Good |
| 10 | 6.31 | 5.64 | – .67 | 33 | 0 | Cholecystitis | Good | Normal | Good |
| 13 | 4.20 | 4.79 | .59 | 34 | 200 | Cholecystitis | Poor | Normal | Death in operating room |
| 27 | 1.22 | 1.85 | .63 | 11 | 0 | Gastric carcinoma | Poor | Moderate damage | Good |

Case 3, no significant change in the hepatic glycogen occurred during operation, even after the longest time interval of 142 minutes between the biopsies had elapsed. All patients were given the same preoperative medication, morphine sulfate ¼ gr. and scopolamine ⅟₂₀₀ gr. The patient who did show a significant drop, Case 3, did not do well at any time after the operation, which was followed by shock. Her course was gradually downhill and respiration ceased on the fourth postoperative day, the final cause of death being massive left pulmonary atelectasis. One of the patients, Case 13, died of a pulmonary embolism while on the operating table. The other patients did well following their operation.

*Relation of Liver Glycogen to Postoperative Course.*—We cannot state whether or not those cases with high liver glycogen had the best postoperative courses. Nineteen had an uneventful postoperative convalescence without fever, nausea, vomiting, or other complications. The average amount of glycogen for this group was 4.04 per cent. Nine patients had fair postoperative courses; that is, they either had temperatures elevated above 100° F., or had nausea, vomiting, or other mild complications. The average percentage of glycogen for this group was 4.11 per cent. Four patients had very poor, stormy, postoperative courses, and their hepatic glycogen averaged 3.17 per cent. The lower percentage of glycogen found in these 4 patients may be significant, but no definite conclusions can be drawn because of the small number of cases studied and the many variable factors involved. The postoperative course of any patient may be upset by numerous factors unrelated to liver glycogen. But in the care of the seriously ill patient food elements cannot be neglected and the value of a high carbohydrate diet in preventing liver damage from specific hepatic toxins and its efficacy in the treatment of hepatic disease has been well shown in animal experiments. Roger,[39] in 1887, first demonstrated the value of glucose in the detoxification of phosphorus by the livers of animals. Beddard,[40] in 1908, first suggested its use in chloroform poisoning. Opie and Alford,[41] in 1915, were the first to show experimentally that a diet high in carbohydrate gives protection against liver damage due to chloroform and phosphorus. Since then their work has been confirmed in the laboratory.[42-53]

That a high carbohydrate diet with a resulting high hepatic glycogen is not the only factor involved in the prevention of liver damage is well known, and that protein is just as important, if not more so, has also been experimentally established. Goldschmidt, Vars, and Ravdin[54] have shown that the severity of liver damage due to chloroform poisoning is primarily dependent on the concentration of lipids in the liver. They believe that the value of a high carbohydrate diet is due to its action in decreasing the amount of lipids in the liver and also due to its protein sparing action. The manner in which a high protein diet acts as a pro-

tector against liver damage is not definitely known although a specific action of methionine has been suggested.[55] Mirski and his associates[44] believe that it is due to intensified glyconeogenesis. Goldschmidt and his co-workers[53] explain the protective action of a high protein diet as "primarily the result of protein available to the liver as a result of the high protein intake." They do not believe that the hepatic glycogen is a factor in preventing liver injury due to chloroform. A high protein diet may be contraindicated in cases which have definite hepatic pathology, since Bollman and Mann[52] have shown that the survival time and general well-being of a dog with obstructive jaundice are increased when fed a high carbohydrate diet, and diminished when fed a high protein diet. Moise and Smith[48] demonstrated that the most active regeneration of liver tissue occurred when the subject was fed a well-balanced stock diet. Stone[42] confirmed this but also found that a high carbohydrate diet was almost as effective, while a high protein diet showed considerably less regeneration of the liver.

Whether or not the protection of the liver from damage due to specific hepatic toxins and its subsequent regeneration is a matter of protein or carbohydrate feeding, and there is evidence of value for both, the practical point is the relative ease with which the carbohydrate intake can be markedly increased just prior to operation. In our patients, supplementary glucose feedings in the twelve hours before the operation raised the glycogen content of the normal livers. In the damaged livers the hepatic glycogen value averaged 2.87 per cent compared to 3.15 per cent for normal livers not receiving supplementary glucose feedings. We feel that 2.87 per cent is a fair value considering the severe degree of liver damage present in our cases. This study helps to confirm the opinion which has long been expressed by many surgeons on the supportive value of a well-chosen preoperative diet in decreasing the stress of long, severe operations and of sustaining the bad risk patient.[56, 57]

## SUMMARY

Biopsies were taken from the liver of 33 patients during their operations and the percentages of glycogen in the liver were determined. The average hepatic glycogen found was 3.96 per cent and the values ranged from 1.1 to 7.56 per cent. Observations were made according to the following groups:

*Group A.*—The average value of hepatic glycogen in patients with normal livers operated upon under spinal anesthesia was 3.15 per cent. The lowest value was 1.1 and the highest was 6.31 per cent.

*Group B.*—When supplementary glucose feedings were given to patients with normal livers in the twelve hours preceding an operation carried on under spinal anesthesia, the average hepatic glycogen rose to 5.03 per cent and the values ranged from 3.19 to 7.56 per cent. Sup-

plementary glucose feedings thus increased the average liver glycogen of Group B 60 per cent over that of the control Group A. This should be of definite value in lessening the stress of long, severe operations and in sustaining the bad-risk patient.

*Group C.*—When supplementary feedings were given to patients with normal livers in the twelve hours preceding an operation carried on under nitrous oxide and ether anesthesia, the average hepatic glycogen value was 4.72 per cent, and the range 3.91 to 5.75 per cent. This average was slightly lower than a similar group (Group B) operated upon under spinal anesthesia.

*Group D.*—With supplementary glucose feedings 4 patients with advanced liver damage showed an average hepatic glycogen of 2.87 per cent and a range of 2.7 to 3.14 per cent.

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# COLON BACILLUS SEPTICEMIA ASSOCIATED WITH ACUTE CHOLECYSTITIS

BENJAMIN LIPSHUTZ, M.D., AND LOUIS KAPLAN, M.D.,
PHILADELPHIA, PA.
*(From the Surgical Service of the Mount Sinai Hospital)*

COLON bacillus septicemia itself is not common, and its association with acute biliary tract disease has been described very infrequently in recent medical literature. The present study is based upon three cases of colon bacillus septicemia associated with acute cholecystitis encountered within a period of fourteen months. Individually these cases presented clinical pictures which made the diagnosis difficult. On reviewing the group certain clinical aspects appeared, which deserve emphasis because of their diagnostic value.

Colon bacillemia may occur in three forms: (1) as an acute and persistent septicemia from the outset; (2) as a temporary bacillemia immediately after trauma, surgical or otherwise, to an area infected with colon bacilli; and (3) as a terminal bacillemia.

The cases to be described are of the first type, an acute colon bacillus septicemia with signs pointing to the gall bladder as the portal of entry. A positive blood culture was obtained in each case prior to operation; hence this was not the fleeting bacillemia which may occur after traumatizing an infected focus, as might be the case if the cultures were taken immediately after operation. Nor was the bacillemia a terminal phenomenon, since two patients are living and well, and the third lived for thirty-five days after the first positive culture.

The infrequency of colon bacillus sepsis may be inferred from the meager literature on the subject. In 1909 Jacob[1] was able to collect but 36 cases from the literature. To these he added 13 of his own. In 3 of his 13 cases and in 15 of the 36 collected cases the biliary tract was indicted as the primary focus. In 1924 Felty and Keefer[2] reported 28 cases of colon bacillus septicemia and reviewed the literature to that date. They were able to identify the portal of entry as urinary, genital, intestinal, or a wound. In none of their cases was the origin from the biliary tract. Since 1924 we have found 39 cases of colon bacillus sepsis reported in the literature.[3] Nine of these cases were apparently associated with acute lesions in the biliary tract such as acute cholecystitis, common duct obstruction, or cholangitis.

## RELATIONSHIP OF COLON BACILLUS TO BILIARY TRACT DISEASE

The role of bacteria in the biliary tract may vary from that of innocuous residency to virulent invasion. Andrews and Henry[4] in 1935

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reported the bacteria found in the gall bladder wall and its contents in 92 cases; the wall was sterile in 57 per cent and the contents were sterile in 67 per cent. *Bacillus coli* was present in the wall in 11 per cent and in the contents in 16 per cent. In 4 cases with obstruction of the common duct, *B. coli* was isolated in 1 case, and *B. coli* and *B. welchii* together in the other 3. If the cystic duct was closed, the acute cases gave positive cultures in 8 of 11 cases, but in the chronic group, the cultures were sterile in 9 out of 10 cases.[5] Andrews' bacteriologic findings indict the *B. coli* as the organism associated with most of his postoperative disasters. It was found in 9 cases; in 3 instances the patients died; a fourth patient developed a large postoperative abscess in the gall bladder bed; in the fifth patient profuse wound suppuration occurred resulting in hernia; the sixth patient had a fever of 105° F. following cholecystectomy; the seventh patient nearly died of paralytic ileus and enormous distention.[5]

Hanssen and Yurevich[6] in 1935 reported the organisms cultured from the biliary tract in 104 cases at operation; 67 per cent were sterile and 33 per cent were infected. The location of the organisms in the infected cases was gall bladder wall, 85.2 per cent; gall bladder bile, 59 per cent; cystic duct node, 38 per cent; gallstones, 24 per cent. In 10 of the 34 infected cases the organism present was the *B. coli.* Hanssen and Yurevich collected the results of cultures of the biliary tract reported by others; *B. coli* was present in from 5 to 54 per cent of the infected biliary tracts. Mailer[7] in the examination of fifty surgically removed stone-bearing gall bladders found *B. coli* in 5 cases.

Aronsohn's experiments[8] in animals indicate that an increase in the number of bacteria in bile seldom produced a reaction in the gall bladder wall when the technique was nontraumatizing. However, in many cases the same organisms injected through the gall bladder wall directly or with accompanying ligation of the common or cystic duct produced severe or even fatal cholecystitis. The latter findings and the bacteriologic findings of Andrews appear to indicate that infection does not become a significant factor in many instances of biliary tract disease unless there is an accompanying erosion of the gall bladder wall by stones or obstruction to the outflow of bile.

Considerable evidence has been brought forth that cholecystitis is not by any means always an infectious process.[9] The stressing of chemical, mechanical, vascular, toxic, and anatomic factors in the initiation of many of the acute gall bladders should not permit one to lose sight of the fact that infection may be superadded and that there is a fair number of acute gall bladders which are of the purely infected type from beginning to end.

How does the infection in the biliary tract cause the septicemia? Is the biliary tract infection a localization of a sepsis originiating from some other focus? In experimental septicemia Chabrol and his asso-

ciates[10] have shown that organisms injected intravenously are excreted by the liver and the kidney in the first six to eight hours.

When there is biliary obstruction, the liver defense against sepsis diminishes, and organisms which would ordinarily have been eliminated rapidly might stay longer in the circulation. One would also expect an accumulation of organisms behind an obstruction in the common duct, and Andrews' findings[5] bear this out.

Lengupta's experiments[11] with intravenously injected colon bacilli possibly elucidate the pathology of the enormous thickening of the gall bladder wall seen in many acute cases but do not indicate an explanation for the sepsis. Intravenous injection of *B. coli* in a normal animal leads to an accumulation of bacteria in the liver and capillary thrombi. In the sensitized, vaccinated, or reinjected animal there is rapid lysis of the injected organisms without definite cellular reaction; the Kupfer star cells do not react. Repeated hematogenous infection of the liver and biliary tract leads to chronic irritation of the gall bladder and biliary tract in which there is infiltration with large lymphocytes and thickening of the walls.

The venous drainage from the gall bladder is into the portal system. When the gall bladder is a focus of infection with *B. coli,* huge numbers of bacteria are probably being poured into the liver directly rather than into the general circulation, as would be the case with a focus in the urinary tract or genital tract. Thus the liver defense may be overwhelmed. This may be the explanation for the extremely toxic condition of these patients.

Patey and Whitby[12] injected bacteria into the portal vein and found the organisms in the general circulation after a few minutes. This would suggest that the liver is only part of the defense against the organisms which enter the portal circulation from the intestine, and that a septic focus draining into the portal system as does the gall bladder may cause a septicemia almost as readily as a septic focus elsewhere; but in most cases the organisms and their toxins are filtered out in the liver and may never reach the general circulation in sufficient numbers for them to be found in blood culture as would be the case if the septic focus were elsewhere.

Colon bacillus infection of the duodenum may have some relationship to biliary tract infection. Grunke[13] was able to recover *B. coli* from the duodenum in 48 per cent of 121 patients presenting symptoms of biliary tract involvement. Colon bacillus infection of the duodenum is most common beyond the age of 40 years; only 11 of 130 cases occurred under the age of 40 years. Similarly the majority of the patients with colon bacillus septicemia associated with cholecystitis are more than 40 years of age. Thus there is a striking parallelism in the age groups of colon bacillus septicemia, associated with cholecystitis, and colon bacillus infection of the duodenum, both are most frequent beyond the age of 40 years.

Summaries of case reports of colon bacillus septicemia associated with acute lesions in the biliary tract in the available literature from 1924 to 1939:

Simon[3a] reported 2 cases of colon bacillus septicemia. The first patient was a female, 63 years of age, who became ill with nausea and vomiting, and then developed jaundice accompanied by chills and fever. She was admitted to the hospital three weeks after the onset. Physical examination at that time showed some enlargement of the liver, red nodules on the legs, and evidence of a peripheral neuritis. The blood culture showed colon bacilli. The leucocyte count ranged from 4,000 to 13,600. There was no elevation of the blood bilirubin. She became progressively worse and was operated upon. A mild pericholecystitis without stones was found, and cholecystectomy was performed. Her fever subsided two days after the operation and she recovered.

The second patient was a female, 50 years of age, who had suffered from cholecystitis for several years. For fourteen days before admission she had severe pain in the right upper abdomen, jaundice, dark urine, light stools, chills and fever. After eight days the right arm suddenly became paralyzed. The pain became milder and the patient became stuporous. On admission the patient was comatose and jaundiced. The abdomen was not tender; the liver was palpable in the midline. The urine showed albumin and casts and was positive for urobilinogen. Blood: R.B.C., 2,700,000; Hgb., 48 per cent; W.B.C., 13,200; 16 per cent young forms. Three days later the leucocyte count was 9,000, 54 per cent young forms. Van den Bergh test: direct positive reaction; the fever varied from 36.9 to 39.7° C. The patient died four days after admission. Post-mortem examination disclosed dense adhesions between the stomach and gall bladder with a gastrobiliary fistula. A suppurative cholangitis was present, the pus containing *B. coli* in pure culture. There were multiple brain abscesses, the pus containing *Staphylococcus aureus* and *B. coli,* the latter predominating.

Sison and Cruz[3b] reported colon bacillus sepsis in a male 20 years of age. The onset was sudden and accompanied by vomiting, epigastric pain, and headache. He gave a history of two previous similar attacks. On admission the temperature was 38° C. The abdomen was slightly tender and rigid in the right upper quadrant. The leucocyte count varied from 15,000 to 21,600. The patient became progressively worse and died shortly after admission. The blood culture made eight hours ante mortem showed *B. coli.* The clinical diagnosis was cholecystitis, cholelithiasis, and acute hepatitis. At post-mortem the original focus of infection was found to be in the biliary tract.

Hofer[3c] reported colon bacillus septicemia in a male 51 years of age. The onset occurred three or four days before admission. There was malaise, pain in the liver area, and a fever up to 39° C. On the day before admission the patient became stuporous and jaundiced. On physical examination the jaundice and stupor were seen and there were

convulsions. Aside from slight enlargement of the liver there were no palpable lesions of the biliary tract. The leucocyte count was 16,200 and the blood culture was positive for colon bacillus. The patient died one day after admission and at the post-mortem examination an acute cholangitis was found.

May and Boulin[3f] reported a case of colon bacillus septicemia in a patient with severe jaundice simulating acute infectious jaundice (spirochetosis icterohaemorrhagica). The etiology was not determined.

Melnotte, Pierre, and Farjot[3g] reported a case of colon bacillus septicemia accompanied by jaundice and intermittent fever.

Lemierre, Augier, and Mahoudeau-Campoyer[3k] reported colon bacillus septicemia in a male 74 years of age. The patient became ill six days before admission, complained of severe pain in the right upper quadrant of the abdomen and of chills. The examination on admission showed jaundice and a mass in the right upper quadrant. Temperature was 38.5° C. Urobilinuria was present and a blood culture made two days after admission showed the colon bacillus. Three days after admission the patient improved and the temperature became normal. No operation was performed.

Garcia[3m] reported colon bacillus septicemia in a female 38 years of age. The onset was abrupt and accompanied by chills and fever (101 to 103° F.). Physical examination showed tenderness and a mass in the right upper quadrant of the abdomen. Leucocyte count was 8,000 to 9,000. The patient was treated by biliary drainage by mouth and recovered without complications.

Davis and Turner[3s] reported a colon bacillus septicemia in a female 35 years of age. About two years prior to admission she had been subjected to operation for stones in the gall bladder and common bile duct. The gall bladder had been removed and the common duct had been cleared of all stones and drained by a rubber tube. Recovery was uneventful. One day before admission the patient was seized with violent upper abdominal pain, vomiting, and fever (103.2° F.). After admission she developed slight jaundice and violent chills, and repeated blood cultures showed colon bacilli. Colon bacilli in pure culture were repeatedly found in the urine. Injections of colon bacillus vaccine were given. X-ray of the abdomen disclosed many small calculi in the common bile duct. The patient refused operation after the symptoms subsided and was discharged twenty-three days after admission.

## CASE REPORTS

CASE 1.—Dr. W. W., aged 46 years, a physician, was admitted on April 5, 1937, complaining of malaise, fever, and abdominal pain. He gave the following history: He had been in good health until April 2, 1937, when he began to have pain in the right upper quadrant of the abdomen, suggestive of biliary colic, and accompanied by an elevation of temperature to 102° F. The pain disappeared in about twenty-four hours, but the fever persisted. He became toxic and drowsy and was taken to the hospital.

*Past Medical History.*—Diabetes mellitus for three years, an attack of biliary colic six months before, dypnea on exertion for some time, and recurrent backache for the past six months.

*Physical examination* showed a well-nourished male, drowsy, cyanotic, and dyspneic. Rectal temperature, 104.4° F.; pulse rate, 136; respirations, 42; blood pressure, 114/84. The nasopharynx showed evidence of an acute ethmoiditis. Chest: Fine crepitant rales were found at the bases of both lungs with diminution of resonance. Abdomen: Moved with respiration, reflexes present, no palpable masses, no definite tenderness, no rigidity of the muscles except for an increase in resistance to pressure in the right upper quadrant, and marked diffuse distention. Urine: Acid, specific gravity, 1.011; trace of albumin; sugar, 1.1 per cent, acetone, plus 2; W.B.C. 2 to 3; occasional fine and coarsely granular casts; occasional hyaline casts. Blood: Hb., 100 per cent; R.B.C., 5,260,000; W.B.C., 33,800 with 92 P.M.N. (44 nonsegmented, 48 segmented); blood sugar, 300; urea nitrogen, 19.6; $CO_2$ combining power, 54 volumes per cent.

Tentative diagnosis on admission: lobar pneumonia, diabetes mellitus, myocardial impairment, chronic biliary tract disease. The abdominal signs appeared to be accounted for by the pulmonary pathology.

Chest x-ray on the day of admission showed no evidence of pulmonary consolidation or pleural effusion, and the diaphragms were normal. A blood culture made on the same day showed a growth of *B. coli.* An electrocardiogram indicated severe myocardial disease.

The patient was treated by administration of glucose and saline solution parenterally, insulin, oxygen, and other supportive medication. Small amounts of carbohydrates were given orally. From April 5 to April 9, 1937, his condition improved. The temperature, pulse, and respiratory rate fell to 100.6° F. rectally, 90, and 26, respectively, and the abdominal distention subsided. Another blood culture showed *B. coli.*

On April 10 he again became drowsy and restless and the temperature rose. On April 11 he became more toxic and irrational and the temperature rose to 104.6° rectal. Abdominal examination disclosed only some resistance in the right upper quadrant. There was no evidence of a lesion acute enough to account for the septicemia, although a biliary lesion was considered. A transfusion was given. Chest x-ray showed no changes except for a few small, poorly defined areas suggesting early bronchopneumonia. On April 12 his condition became even worse and he appeared to be in extremis. Abdominal examination now disclosed a mass in the region of the gall bladder. A scout x-ray film of the abdomen showed only gaseous distention of the stomach. A cystoscopy done to exclude a lesion of the right kidney was negative. After another transfusion the patient was subjected to an exploratory operation under local anesthesia. An acute gangrenous cholecystitis was found. The gall bladder had perforated, and abscesses had formed contiguous to it in the liver. The gall bladder was removed, clamps being left on the cystic duct, artery, and some smaller vessels because the tissues were too necrotic to hold ligatures. The wound was packed.

The patient was practically moribund. He improved slightly after a transfusion in the evening, and after another transfusion on the following day he was definitely on the mend.

Culture of the cystoscopic urine showed *B. coli* and culture of the bile obtained at operation showed *B. coli* and *B. welchii.*

Attempts to prepare a bacteriophage for the colon bacillus failed. Blood cultures made on April 14 and on April 19 showed no growth. Treatment was continued by parenteral fluids; insulin, etc., and carbohydrates by mouth were started late on April 13. By April 15 he was definitely out of danger, and the clamps in the wound were removed. There was no hemorrhage, but there was marked drainage of purulent material which decreased daily. Another transfusion was given

on April 16, and he proceeded to recover without any further complications. On April 27 he was allowed out of bed, the temperature being almost normal, and on May 11 he was discharged in good condition.

Pathologist's report on the gall bladder: "Gangrenous cholecystitis with suppurative pericholecystitis."

CASE 2.—S. M., a white male, 48 years of age, was admitted on May 2, 1937, complaining of fullness and discomfort in the upper abdomen for three days and an acute attack of epigastric pain, nausea, and vomiting for two and one-half hours.

*History.*—He had been in his usual health until three days previously, when he awoke feeling "out of sorts." Following breakfast he developed a marked sense of fullness and distress in the upper abdomen with some reference to the right shoulder. Later in the day he was given an enema and a saline purge. He felt somewhat improved until 7:00 P.M. on the night of admission when he again began to have epigastric discomfort and pain which became progressively more severe. Nausea and vomiting followed. His physician had him taken to the hospital immediately.

*Physical examination* showed a well-developed, dark-complexioned middle-aged male, drowsy, and apparently acutely ill. Temperature, 101° F.; pulse, 120; respirations, 20; blood pressure, 120/80; head, neck, and chest were negative. The significant findings were abdominal; a marked distention with a tense abdominal wall. Determination of tenderness was unsatisfactory because of prior administration of morphine. A marked increase in muscle tonus was present in both upper quadrants. Peristalsis was heard throughout. The abdominal reflexes were absent. Urine: acid, specific gravity, 1.021; very faint trace of albumin; 2 to 4 W.B.C. Blood: W.B.C., 16,400; polymorphonuclears, 87 per cent.

Tentative diagnosis: cystic duct obstruction with acute suppurative cholecystitis.

Symptomatic treatment was given. On the following day (May 3) the temperature remained about 102° F. He felt slightly improved. An electrocardiogram indicated myocardial damage but no infarction. Blood count: Hb., 90 per cent; R.B.C., 4,540,000; W.B.C., 10,250; polymorphonuclears: 91 per cent.

On May 4 abdominal x-ray showed a distention distal to the hepatic flexure, indicating a colon lesion at that point or a lesion in the right upper quadrant. A blood culture was reported positive for *B. coli.* The abdominal pain became much more severe. Physical examination of the abdomen at this time disclosed a very tender tense mass in the right upper abdomen. At noon there was a severe chill with a rise in temperature to 105° F. A diagnosis of gangrenous cholecystitis was made and an emergency operation was performed about 5:00 P.M. after the administration of glucose and saline solution.

Under spinal and nitrous oxide anesthesia a right subcostal incision was made and a large distended gall bladder was exposed. The liver was dark and large. The gall bladder was aspirated and then removed after ligation and division of the cystic duct and artery. A gauze drain was put down to the gall bladder fossa of the liver and the abdomen was closed. Subsequently culture of the gall bladder bile showed *B. coli.* Anaerobic culture showed no anaerobes.

The patient received a transfusion of 300 c.c. of whole blood immediately after operation. Sufficient glucose and salt solution was given in the following thirty-six hours. On May 5 (the day after operation), catheterization was necessary. On May 6 the temperature dropped to 100° and a slight jaundice developed. Blood: Hb., 100 per cent; W.B.C., 17,900; polymorphonuclears, 84 per cent; sugar, 198; urea, N. 24.2; chlorides, 524; icterus index, 12.8. The symptoms cleared up promptly and the temperature was normal on May 9. He was discharged on May 17 in good condition. Pathologist's report on gall bladder: Wall average in thickness, mucosa appeared normal. Microscopic examination: "Chronic cholecystitis."

CASE 3.—Mrs. J. R., aged 65 years, was admitted to the hospital on June 5, 1938, complaining of fever and pain in the back. She gave the following history: She had been well until one week before admission, when she began to have chills, fever, and sweats, said by her physician to resemble those of malaria. These recurred daily. On the day before admission she began to have pain in her back, which persisted. There had been no respiratory, gastrointestinal, or urinary symptoms.

*Physical examination* showed an elderly white female, dyspneic, and exhibiting marked cyanosis. Temperature, 102.4°; pulse rate, 140; respirations, 30; blood pressure, 170/74. Head: negative, except for slight fetor oris. Chest: a few rales in the left lung base, auricular fibrillation with pulse deficit. Abdomen: marked distention, palpation very difficult. Liver palpable, slightly below the costal margin. An umbilical hernia of moderate size, reducible, was present. Tentative diagnosis on admission: Septicemia of unknown origin, possible pyelitis, hypertensive cardiovascular disease, umbilical hernia. Urine: acid, specific gravity, 1.010; trace of protein; 8 to 10 W.B.C.; occasional R.B.C., very occasional hyaline and fine granular casts. Blood: Hb., 90 per cent; R.B.C., 4,660,000; W.B.C., 23,700; polymorphonuclears, 89 per cent; blood sugar, 100; blood urea nitrogen, 31; icterus index, 18; van den Bergh test, very faint biphasic reaction. A blood culture made on June 6 showed *B. coli*.

The patient had chills and fever for the next few days. The abdominal findings were practically nil until June 9, when marked tenderness and rigidity were noted in the right upper quadrant. Jaundice became visible. Sulfanilamide gr. xx four times daily had been started on June 5. It was discontinued on June 9.

The patient was given glucose parenterally and was then operated upon without further delay (June 9). Under local anesthesia, supplemented by small amounts of nitrous oxide and oxygen, a right subcostal incision was made. The gall bladder was gangrenous and had perforated. The necrotic gall bladder was removed down to the ampulla, into which was fixed a rubber tube. A gauze drain was placed in the hepatic gall bladder bed.

*B. coli* was isolated from the bile removed at operation. Anaerobic cultures showed no anaerobes. Immediately following operation the patient received a transfusion and glucose and saline solution parenterally. In the next few days her temperature remained high (103 to 104°). She then improved and a transfusion was given on June 11. On June 12 her jaundice was much less, her heart was not fibrillating, and she was taking liquids well. The wound was draining profusely. Abdominal x-ray (scout film) on June 4 showed considerable gaseous distention of the stomach with slight gaseous distention of the transverse colon. The diaphragms appeared normal.

On June 16 she became worse. A blood culture showed no growth. For the next few days she again had chills. Her condition continued septic and downhill. On June 20 another blood culture showed no growth. On June 23 chest x-ray showed no abnormalities of the lungs or diaphragm. Blood culture on June 25 showed no growth. On June 28 the draining sinus was injected with sodium iodide. X-ray showed a tract 12 cm. in length and 1 cm. wide and gave no other information. Another transfusion was given on June 30. Her condition continued unchanged except for a moderate fall in the level of fever. On July 5 a transfusion was given. On July 6 the fever increased and by July 10 the level was 103 to 104°. No definite focus of suppuration could be identified. A subhepatic suppuration was suspected, and since the patient was still losing ground, the wound was opened under nitrous oxide anesthesia on July 12. No definite lesion was found. Early on the following morning she had an abrupt rise in temperature (105° rectally) and pulse rate (160). The blood pressure was 85/70. She became irrational and pulseless and died about twenty-four hours after her second operation. Blood culture taken July 10 was negative.

Pathologist's report on gall bladder: "Acute gangrenous perforated cholecystitis; cholelithiasis."

*Autopsy Findings.*—Gastrointestinal tract: stomach, moderately distended; small intestines, moderately distended and covered by a thin layer of exudate; colon, normal; liver and gall bladder, cystic duct dilated; common duct slightly dilated; bile, dark, not purulent; liver, large, no abscesses; microscopic, hemorrhagic hepatitis, widespread, advanced, cloudy swelling, fatty infiltration; spleen, large, soft, pulpy, and dark. A localized collection of pus was present at its root in contact with the pancreas. It was walled off by the splenic surface and the regional fat. Adrenals, medullary degeneration: kidneys, cloudy, swelling in right, left, in addition to cloudy swelling, showed two cortical abscesses 2 mm. and 3 mm. in diameter.

### COMMENT ON PRESENCE OF B. WELCHII IN BILIARY TRACT

The presence of the *B. welchii* in the wall and contents of the biliary tract without the signs and symptoms of gas gangrene has been variously reported. *B. welchii* has been found in normal bile at autopsy. This association was noted by Branch who pointed out that this microorganism, which is indigenous to areas drained by the portal system, is apparently held in abeyance by healthy living tissues. Andrews regards the *B. welchii* as of no significance, although he notes it may be present in the gangrenous gall bladder. In 210 cases in which gall bladder was removed at operation, Branch found the *B. aerogenes capsulatus* in the wall of the gall bladder in 8 cases; in the bile, in 5 cases; and in the stones, in 7 cases. It was never the predominating organism. The *B. welchii* may, however, in rare instances produce a true gas bacillus infection. Graef and Sturtevant found 9 cases of cholecystitis due to *B. aerogenes capsulatus* reported in the literature and added an additional case with post-mortem findings. Of the 10 patients, 5 recovered and 5 died. (For literature on *B. welchii* and its relation to cholecystitis consult Graef and Sturtevant[14] and Lohr.[15])

### COMPOSITE CLINICAL PICTURE

Colon bacillus septicemia associated with acute lesions of the biliary tract starts abruptly in patients who are otherwise in good health. Two of our patients (Cases 2 and 3) were in fairly good health at the time of the onset and had no symptoms referable to the biliary tract. One patient (Case 1) was a well-controlled diabetic who had only a single attack of biliary colic six months before. This was characteristic also of almost all of the cases reviewed in the literature. The first symptom is often pain in the right upper abdomen, which may be very severe, very mild, or rarely so slight as to pass unmentioned, and which may subside rapidly due to gangrene and perforation of the gall bladder (Cases 1 and 3). Chills, high fever, vomiting, and perhaps slight jaundice come on simultaneously or follow in short order. In a few days the patient may become toxic, drowsy, and comatose.

A number of the reviewed cases, as well as our own, exhibited this intense toxemia, accompanied in two or three instances by epileptiform

convulsions. Ordinarily the colon bacillus is not of great virulence, so that the toxemia seems disproportionate. It may perhaps be due to toxic hepatitis with impairment of the detoxifying function of the liver and in part to dehydration.

It might be expected that such a violent infection within the abdomen would be clearly manifested by abdominal symptoms and signs. This is not the case. The abdominal symptoms may be masked by toxemia and drowsiness or coma, and the signs may be masked by distention of the colon and slight reflex rigidity. Case 1 on admission showed a diffuse abdominal distention and a very slight increase in resistance to pressure in the right upper quadrant. Definite signs pointing to the gall bladder, a tender mass in the right upper quadrant, did not appear until seven days after admission. Case 2 on admission exhibited marked abdominal distention and an increase in tension of the abdominal muscles, mainly in the upper quadrants. Two days later a tender mass was found in the right upper quadrant. Case 3 on admission also showed striking abdominal distention. There were no other signs except for a palpable liver. Not until four days later did tenderness and rigidity appear in the right upper quadrant. In retrospect, the significant finding was the distention.

The laboratory findings include not only blood cultures positive for *B. coli* in the three cases, but also cultures of *B. coli* from the gall bladder bile. In Case 1 *B. welchii* was also found in the gall bladder bile. In this case the urine obtained during cystoscopy also showed colon bacilli. The leucocyte counts on admission varied over a wide range: Case 1: 33,800 polymorphonuclears, 92 per cent, 44 nonsegmented, 48 segmented; Case 2: 16,400 polymorphonuclears, 87 per cent; Case 3: 23,700 polymorphonuclears, 89 per cent. Elevation of the icterus index was recorded in 2 cases, and it was probably toxic in origin.

### DIFFERENTIAL DIAGNOSIS

The relative insignificance of signs pointing to the gall bladder made identification of the true condition very difficult. In Cases 1 and 3 the signs at the lung bases and the abdominal distention suggested early pneumonia, possibly pyelitis, as the cause of the symptoms. The signs at the lung bases were explained later by the biliary lesions. Diaphragmatic irritation or inflammation is common in acute suppurative biliary tract disease, and after perforation of the gall bladder, actual subphrenic suppuration is not rare. The local peritonitis explained the distention.

After the primary focus was removed, the sepsis subsided quite rapidly. In Case 3 the persistent fever was due probably not to sepsis, since repeated blood cultures were negative, but to a purulent collection about the spleen. Metastatic abscesses were identified only in the fatal case, two very small ones in the left renal cortex.

## TREATMENT

The most important factor in the treatment of a septicemia is the attack on the primary focus. In these cases identification of the gall bladder as the primary focus was followed by cholecystectomy. An unquestionably moribund patient was thereby saved (Case 1) and prompt subsidence of the infection occurred in Case 2. The fatal termination in Case 3 seems due rather to perforation of the gall bladder and subphrenic abscess than to septicemia. An earlier diagnosis and a prompt operation might have saved this patient.

The value of parenteral administration of fluids to correct dehydration and of transfusion for anemia and its supportive effect must not be underestimated.

## SUMMARY

1. Three cases of colon bacillus septicemia associated with acute cholecystitis have been presented. These cases are characterized by abrupt onset of severe or mild abdominal pain, accompanied by chills, fever, and intense toxemia. After a few days signs pointing to the primary focus in the gall bladder may be so masked as to make diagnosis extremely difficult.

2. The literature on this subject has been briefly reviewed.

3. Prompt cholecystectomy appears to be the treatment of choice.

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# PERITONEOSCOPY*

RICHARD T. SHACKELFORD, M.D., BALTIMORE, MD.
*(From the Surgical Services of the Johns Hopkins and Union Memorial Hospitals)*

PERITONEOSCOPY has attracted a good deal of attention in the recent American literature. It is a simple and relatively safe method of visualizing certain of the intraperitoneal organs or of obtaining a biopsy, if necessary, to establish a diagnosis. In selected cases it can replace the more serious procedure of an exploratory laparotomy. Whenever suitable this is a desirable substitution, for it is a minor procedure, performed under local anesthesia with a minimal risk and expense, requiring but one day's hospitalization as contrasted with the two to three weeks' hospitalization required for a laparotomy as well as its higher mortality and greater discomfort.

Peritoneoscopy is not a new procedure but originated in 1901. In that year Ott,[1] a Russian, inserted a speculum through a small incision in the abdominal or vaginal wall and by means of a head mirror inspected the peritoneal cavity and its contents. In the same year and independently Kelling,[2] in Germany, described a technique for what he termed coelioscopy. His technique was quite similar to the one now generally used and consisted of first creating a pneumoperitoneum with a small blunt needle, then inserting a Nitze cystoscope into the abdominal cavity and inspecting its contents. The method had been used only on dogs and was overlooked by the medical profession at large. In 1910 Jacobaeus,[3] of Stockholm, unaware of Kelling's work, published an identical procedure by which he had inspected the peritoneal cavities of 17 patients with ascites. Jacobaeus made several subsequent reports recommending the procedure, and although Kelling later recorded his use of the method in human beings, the former's name became more closely associated with laparoscopy, as he termed it. In 1911 Bernheim[4] at the Johns Hopkins Hospital examined the peritoneal cavity of 2 patients by means of inserting a small bore proctoscope through the abdominal wall and inspecting the various organs. He called this method organoscopy. Although successful, it was not well received and its use was abandoned.

The present interest in the subject has been aroused chiefly by the convincing work of Ruddock,[5] of California. He has published a large series of examinations with such success that the method has become firmly established as a diagnostic procedure. I have been able to collect the reports of over 2,000 peritoneoscopic examinations performed by twenty-two different operators. In this total series there have been 2 deaths, 1[5] of which was due to hemorrhage from a biopsy wound in

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the liver. This occurred in the days before a method of coagulating the wound to prevent such a mishap had been devised. The second fatality[6] occurred in a moribund patient whose general condition was too feeble to withstand any further manipulation. In the above collected 2,000 cases there have been 11 instances in which the intestine has been accidentally perforated during the procedure and in no case did any fatality or serious complication develop. Except for a few examples of subcutaneous emphysema no other complications or accidents have been reported.

## TECHNIQUE

I have been performing peritoneoscopies since early in 1938. The instrument used has been the Ruddock peritoneoscope which has been found satisfactory in every respect but one; namely, it would simplify the taking of biopsies if the biopsy forceps could be fitted with a sliding collar as is the observation telescope. By this means the forceps could be slid back and forth within the metal sheath instead of sliding the sheath through the skin as is now necessary. The examination has always been carried out in a darkened operating room under strict aseptic precautions. The technique has followed that of Rubbock[5] which need not be redescribed. I have found it helpful to lubricate the tip of the pneumoperitoneum needle and the trocar with sterile glycerine, as it is a distinct aid in their passing through the tissues. When the nature of the lesion could not be determined by inspection alone, a piece of that tissue was removed for histologic study. This was necessary in about one-fourth of the cases examined.

## CONTRAINDICATIONS

There are certain types of cases in which peritoneoscopy should not be used. These are as follows:

1. Acute abdominal inflammatory disease. Here the danger of spreading the infection is prohibitive.

2. Abdominal distention. In these cases the intestinal wall is thinned out by distention and is too vulnerable to the possibility of perforation by the advancing needle or trocar.

3. Known intra-abdominal adhesions. This type of case is not an absolute contraindication for many times by means of entering the abdomen at a site some distance from the adherent area the examination can be satisfactorily and safely carried out. It must be remembered, however, that all the known accidental perforations of the intestine have occurred in this group.

## INDICATIONS

Peritoneoscopy should be performed only with a specific purpose in mind. It should be used to establish a differential diagnosis, to con-

firm a clinical impression, or to determine the presence, extensiveness, and nature of a suspected mass. It will often disappoint if used only for a general tour about the abdomen without such a specific purpose in mind.

In the usual case the greater part of the surface of the liver, the fundus of the gall bladder, the anterior wall of the stomach, colon, the surface of the omentum, and the parietal peritoneum are easily visualized with the patient supine. The spleen is not seen when normal in size unless the patient is placed on his right side, in which case its tip comes into view. If enlarged it can readily be examined in either instance. By placing the patient in the Trendelenburg position, both tubes, ovaries, fundus of the uterus, cul-de-sac of Douglas, and posterior peritoneal wall of the bladder can be examined. The appendix is only rarely observed, while the pancreas and kidneys are never seen, although a tumor of either may project or extend into the field of vision. As a result we have found the greatest use of the procedure in establishing the diagnosis of cirrhosis or malignancy, either primary or secondary, of the liver; tuberculous peritonitis; determining the operability of carcinoma of the stomach; and identifying various lesions of the female pelvic organs. It also would seem that in all cases of ascites, peritoneoscopy should be performed at the time of abdominal paracentesis, as the procedures are identical, and a positive diagnosis can be established without additional risk or discomfort.

## RESULTS

My personal results are best seen by consulting the first column of Table I. In the second column of that same table, for the purpose of comparing experiences, are listed the number of cases reported in the literature in which the same lesion has been recognized by other operators. There have been many additional conditions identified by these authors which are not included, as the list would be too long.

A word of explanation should be made of a few of these groups. The 3 cases of normal pregnancy were individuals known to be pregnant but in whom an ectopic pregnancy was suspected. This suspicion was disproved and they went on to a normal delivery at the proper time. The carcinomas of the pancreas were not seen directly but were diagnosed by the histologic study of a biopsied malignant extension. The carcinomas of the rectum had been previously identified by local biopsy, but peritoneoscopy showed their inoperability due to the presence of metastases in the liver. The 2 cases of operable carcinoma of the stomach were in patients known to have a large filling defect in the stomach and both of whom had an easily palpable abdominal mass. In each instance the condition was considered to be clinically hopeless, but peritoneoscopy revealed no metastases to the liver or omentum, and they were both later successfully resected.

TABLE I

| | SHACKELFORD'S SERIES | COLLECTED FROM LITERATURE |
|---|---|---|
| Normal abdomen | 14 | 72 |
| Cirrhosis of liver | 10 | 334 |
| Carcinoma of ovary | 8 | 79 |
| Peritoneal implants | 6 | 105 |
| Fibroid uterus | 4 | 47 |
| Metastases to liver | 4 | 167 |
| Adhesions | 4 | 75 |
| Carcinoma of pancreas | 4 | 8 |
| Hydrops of gall bladder | 4 | 31 |
| Ectopic pregnancy | 3 | 63 |
| Normal pregnancy | 3 | 19 |
| Carcinoma of gall bladder | 2 | 9 |
| Carcinoma of rectum | 2 | 4 |
| Carcinoma of stomach, operable | 2 | 83 |
| Tuberculous peritonitis | 2 | 52 |
| Ovarian cyst | 2 | 63 |
| Peptic ulcer | 1 | 6 |
| P. I. D. | 1 | 49 |
| Failure of examination | 3 | |
| Incorrect diagnosis | 2 | |
| Total | 81 | |

## COMPLICATIONS

There have been no deaths in my series and only 2 in the over 2,000 cases reported. In one of my cases the intestine was perforated with the trocar. It was immediately repaired by suture and no sequelae developed. Ten other such mishaps have been reported, but convalescence was uneventful in each. In 9 of these the wounded intestine was immediately sutured, but in the other, which was perforated by the pneumoperitoneum needle, the needle was simply withdrawn and no attempt at repair made.

In another of my cases subcutaneous emphysema was an annoyance for six days but subsided spontaneously. No other complications have occurred.

Biopsies were taken in about one-fourth of the cases without any harmful effects.

There were 3 failures and 2 incorrect diagnoses made. The first was the one in which the intestine was perforated and the examination was not completed. In 2 other cases dense intra-abdominal adhesions prevented carrying out the procedure. In another of my early cases in which an abdominal mass was present, I stated no metastases could be seen; however, later operation showed numerous small nodes in the omentum which the peritoneoscopist had not recognized, although they had been seen. In another instance I was again at fault in diagnosing an ovarian cyst in what turned out to be a distended loop of sigmoid caught by a band of adhesions. This illustrated the point that only those lesions which can be identified positively should receive a positive

diagnosis, and if in doubt, the tissue should be biopsied, or if that is undesirable, it should merely be described. No further mistaken positive diagnoses have been made.

## PRACTICAL RESULTS

So far the discussion has centered on the academic side of medicine, concerning mainly the technique and possible diagnostic scope of the procedure. However, the method has practical value as well. By its means we have prevented the performance of what would have been 27 useless laparotomies. In addition, 10 patients in whom operation was not being considered were found to have lesions requiring surgical intervention. In the remaining 44 patients a suspected diagnosis was confirmed and the contemplated therapy carried out with the assurance gained by the removal of all doubts as to its correctness.

## SUMMARY

1. Peritoneoscopy is a relatively safe and minor procedure.

2. Its greatest value is in diseases of the liver, pelvic organs, tuberculous peritonitis, and for the determination of the nature and extent of malignant tumors.

3. It should not be used in cases with acute inflammatory conditions, abdominal distention, or multiple adhesions.

4. It should be used only with a definite purpose in mind as to make a differential diagnosis, to confirm a suspected diagnosis, or to identify and localize a tumor.

5. By its means some patients were spared a useless laparotomy and a fewer number previously considered inoperable were found operable. In others therapy could be forced more vigorously when all doubts as to the correct diagnosis had been removed.

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# TRANSTHORACIC, TRANSPLEURAL LIGATION OF THE FIRST PORTION OF THE LEFT SUBCLAVIAN ARTERY

## A Report of the First Case

Arthur S. W. Touroff, B.S., M.D., New York, N. Y.
*(From the Surgical Service of Dr. Harold Neuhof, the Mount Sinai Hospital)*

### INTRODUCTION

THE FIRST portion of the subclavian artery extends from the point of origin of the vessel to the inner border of the anterior scalene muscle. The right subclavian arises from the innominate artery at the level of the sternoclavicular joint. Thus, its first portion is short and relatively superficially placed. Since it often rises above the level of the inner end of the clavicle, it usually can be ligated readily through a supraclavicular approach. By contrast the left subclavian arises from the aortic arch and ascends through the superior mediastinum to the root of the neck. Its first portion thus lies deeply within the thorax. In order to ligate this portion of the vessel, the surgeon must either work at a considerable depth through a supraclavicular incision or approach the vessel more directly by removing portions of the clavicle and sternum or upper ribs.

Ligation of the first portion of the subclavian artery was first performed by Colles[1] in 1813. On that occasion, through a supraclavicular approach, he tied off the vessel on the *right* side in a patient suffering from traumatic subclavian aneurysm. In commenting upon his case, Colles expressed the opinion that ligation of the first portion of the *left* subclavian was impracticable because of difficulty of access and the danger of injuring the adjacent pleura, internal jugular vein, and common carotid artery. It is interesting to note that at the time, practically all contemporary British surgeons and anatomists concurred. In 1845, however, Rodgers[5] succeeded in ligating the first portion of the *left* subclavian and called attention to the danger of injuring the thoracic duct and the pleura during the course of the procedure. Stimulated by the surgical exploits of Colles and Rodgers, ligation of the first portion of the right and left subclavian was attempted by others; and the operation, although not performed frequently, became firmly established.

Although the early observers were proved incorrect in their assumption that ligation of the first portion of the left subclavian was impossible, the procedure nevertheless was, and still remains, difficult and hazardous. In this connection the reports collected by Halsted[3] of 22 such attempts made between 1845 and 1924 are significant. In only 7 of these 22 cases could the vessel be approached through a supra-

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clavicular approach, by dividing the soft parts alone. In the remaining 15 cases operation involved resection of the clavicle in 6, resection of the clavicle and portions of the sternum in 4, and resection of the clavicle, sternum, and first rib in 4. In the final case (Sherrill[6]) the vessel was approached extrapleurally through a posterior thoracic incision with resection of the second, third, and fourth ribs. It is important to point out that ligation of the first portion of the left subclavian is difficult not only because the vessel is situated largely within the thorax, but also because the procedure at times is complicated by abnormalities referable to the condition for which ligation is performed. In the cases collected by Halsted, ligation was necessitated by an aneurysm of the subclavian artery in all but one. (In the latter, the lesion was a malignant tumor which occupied the supraclavicular fossa.) In the presence of an aneurysm, ligation of the subclavian is apt to be attended with serious hemorrhage as the result of accidental injury of the aneurysm itself and from numerous adjacent collateral vessels which must be traversed during the course of operation. Other complications, reported in the cases collected by Halsted, include operative shock, injury to the thoracic duct, brachial plexus and pleura, and hemorrhage (sometimes fatal) from adjacent large vessels, such as the left common carotid artery, left internal jugular vein, and left innominate vein. Additional objectionable features of operation are that it (1) is usually time-consuming, and (2) is apt to be followed by appreciable deformity if the removal of substantial portions of bone is necessary. Thus the conventional method of ligation presents a number of serious disadvantages and dangers.

## CASE REPORT

Recently the author was confronted with a case of diffuse, congenital arteriovenous aneurysm involving the left upper extremity in a child 13 years of age. Operation had been advised because of increasing cardiac insufficiency. The procedures which previously had been performed consisted of double ligation of the axillary artery and vein, excision of an axillary arteriovenous communication, and an attempt at ligation of the third portion of the subclavian artery. Because of profuse hemorrhage from numerous collateral vascular channels which involved the entire supraclavicular region and root of the neck, it had been necessary to discontinue the last operative procedure before the vessel was exposed. In view of this bleeding it seemed fair to assume that further attempts to ligate any portion of the subclavian through the conventional surgical approach again would be attended by ominous hemorrhage. Accordingly, the only safe method appeared to be to approach the vessel at some distance from the area in which collateral circulation existed. It seemed that this could be accomplished most readily by exposing its first portion through a transthoracic, transpleural incision made at some distance from the previous operative site. Although the merits of such a surgical approach appeared obvious, a search of the literature failed to disclose any reference to its use in subclavian ligation. In operating upon cases of patent ductus arteriosus, the author[7] previously had employed the anterior, transthoracic, transpleural incision advocated by Gross,[2] and had been impressed with the excellent exposure of the left subclavian as it took origin from the aortic arch. This also was noted during the perform-

ance of left pneumonectomy through the anterior approach advocated by Rienhoff.[4] Accordingly it was decided to employ a similar incision in the present case.

Operation was performed on Sept. 24, 1940, under cyclopropane anesthesia administered through a snugly fitting face mask. The patient was placed on her back with sand bags beneath the left hip and shoulder, and the arm was extended at a right angle in order to permit access to the axilla. A hockey-stick incision was made in the second intercostal space on the left side, with its long arm extending from the edge of the sternum to the anterior axillary line. The short arm of the incision was carried upward along the edge of the sternum to the lower border of the first rib. The second and third costal cartilages were divided close to the sternum and the internal mammary vessels ligated and divided at the upper and lower limits of the operative field. The incision in the second intercostal space was deepened down to the pleura and the latter opened freely. The second and third ribs were separated widely with the Lilienthal rib spreader and the lung permitted to collapse out of the field of vision. The aorta then was readily seen and the left subclavian artery easily could be followed upward to the summit of the chest from its point of origin on the convexity of the aortic arch. The left common carotid could not be visualized. A short, vertical incision was made in the mediastinal pleura over the lowermost portion of the subclavian and the vessel freed by blunt dissection. Two strands of heavy, braided silk next were passed beneath the vessel with a ligature carrier. Before tying these ligatures, the subclavian was compressed, and the carotid pulse was sought in the neck. After ascertaining that carotid pulsation was present, the subclavian ligatures were tied securely, the first, about one-half inch from the aorta, and the second, about one-fourth inch further distally. The incision in the mediastinal pleura was left open in order to permit the escape of fluid into the left chest. The ribs were brought together with pericostal sutures of chromic catgut and the thoracic parieties closed in layers without drainage. The lung was inflated under positive pressure by the anesthetist as the thorax was closed. Although there was bleeding from collateral vessels in the skin and muscle during operation, it presumably was much less than would have occurred had the approach been made through the conventional supraclavicular incision. The child stood the procedure well and left the operating table in good condition.

Small amounts of serosanguineous fluid were aspirated from the left chest on three occasions during the week following operation. Convalescence from the procedure otherwise was uneventful. (The further course is not relevant but the case, which was of unusual interest and ended in recovery, will be reported in a separate communication.)

## DISCUSSION

Because of the relative infrequency of surgical conditions (chiefly hemorrhage and aneurysms) of the subclavian artery, the subject of ligation of the first portion of this vessel is perhaps of only minor interest to most surgeons. During time of war, however, it takes on new importance. Thus, experience in World War I indicates that in the present conflict, gunshot and other penetrating wounds of the subclavian vessels will be not infrequent. While in some cases hemorrhage will result in early mortality, in others the bleeding may be checked sufficiently to permit transportation of the patient to a hospital. Experience indicates further that those patients who do not succumb to massive subclavian hemorrhage usually develop large hematomas which render subsequent attempts at surgical ligation extremely difficult and hazardous. Because of these hazards (especially

uncontrollable hemorrhage) many surgeons during World War I deemed it wise never to operate upon such patients. The result was that many of the latter subsequently succumbed either of infection or secondary (infective) hemorrhage; or, if sufficiently fortunate to survive, developed an arterial or arteriovenous aneurysm.

The method of ligation herein described appears to be well suited to the treatment of certain wounds of the subclavian vessels, for it permits rapid exposure and ligation of the vessel in an area far removed from the site of injury. Once hemorrhage has been controlled, the local site of injury can be explored and débrided freely. In cases in which there is evidence that injury to the subclavian vessels is complicated by adjacent intrathoracic trauma, the procedure has the added advantage of permitting direct visualization and an attempt at treatment of the intrathoracic component of the wound.

In cases of injury of the right subclavian artery, when exposure of the vessel through the conventional approach is difficult or unsafe, or in cases of injury of the innominate artery, a right-sided transthoracic transpleural approach might be attempted for ligation of the innominate artery.

In certain cases of traumatic aneurysm of the first or second portion of the subclavian artery, the methods of subclavian and innominate ligation which have been described may result in cure alone or may be employed as a preliminary to subsequent excision or distal ligation. Likewise in the rare case of nontraumatic aneurysm of the very first portion of the left subclavian or innominate artery, the transthoracic, transpleural approach appears to afford a good exposure for direct surgical attack (either ligation or excision) upon the lesion.

## SUMMARY AND CONCLUSIONS

1. The case herein reported appears to represent the first attempt at transthoracic, transpleural ligation of the first portion of the left subclavian artery to be recorded in the literature.

2. This approach to the first portion of the left subclavian artery permits rapid and free exposure of the vessel proximal to its branches.

The experience of surgeons who have operated upon cases of patent ductus arteriosus through such an approach has already demonstrated that it is not attended with appreciable shock (even in debilitated children suffering from cardiac insufficiency).

Removal of portions of the clavicle, sternum, and ribs is not necessary. The exposure, therefore, is not apt to be time-consuming nor followed by deformity.

There is no danger of injury to the thoracic duct, brachial plexus, or adjacent large vessels at the root of the neck.

The procedure is recommended in cases in which ligation of the first portion of the left subclavian is necessary alone or in combination with another procedure, or as a preliminary procedure.

In view of the fact that operation upon the innominate artery, and at times upon the proximal portion of the right subclavian artery, presents difficulties and dangers similar to those encountered in exposing the left subclavian, ligation of the innominate artery through a transthoracic, transpleural approach carried out on the right side might be attempted in certain cases.

The incision described also appears to afford the best approach for direct surgical attack upon an aneurysm involving the very first portion of the left subclavian or innominate artery.

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# RECURRENCES AND FAILURES FOLLOWING THE MODERN TREATMENT OF VARICOSE VEINS

P. J. SARMA, M.D., CHICAGO, ILL.

*(From the Department of Surgery, University of Illinois College of Medicine and Ravenswood Hospital)*

NOTWITHSTANDING the important improvements made in the modern treatment of varicose veins, recurrences and failures occurred in almost 16 per cent of the patients treated by us from January, 1935, to January, 1940. Recurrences were greater in my own service nine years preceding that period. The recognition of the absolute necessity of ligating the saphenous vein when there was incompetency of the saphenofemoral valve was alone responsible for a reduction in the percentage of recurrences in our early work.

We recognize that even with the most careful treatment there is a certain tendency toward recurrence in some patients and also a tendency to develop a new group of varicosities. So far we have been unable to prevent re-formation of varicosities in these patients. Even considering all these factors, I believe the percentage of recurrences could be minimized by careful, critical studies.

For this presentation I have reviewed 230 patients with recurrences and failures who were treated by me or under my direct supervision. The patients who were treated elsewhere, but who consulted us for further treatment of recurrences, were purposely excluded.

For simplification of our study these patients were classified in two groups: (a) those who had only injection of sclerosing solutions, and (b) those who had ligation followed by obliterative treatment.

Ninety-eight patients belonging to this first group were studied.

The record shows that 33 patients who were diagnosed as having simple dilatation of the superficial veins and who were successfully treated with sclerosing solution returned one to five years afterward with recurrences. Examination revealed that they all had developed incompetency of the saphenofemoral valve during this interim. High ligation and further obliterative treatment were advised.

Eighteen patients were previously diagnosed as belonging to the Trendelenburg positive group and ligation was advised. They refused operation and were treated by injection. Fifteen of these patients showed a fair obliteration after injection, but canalization developed within a very short time. Fourteen patients of this latter group were eventually ligated and benefited. For the last three years we have made it a rule not to give injection treatment as a palliative measure if ligation is refused.

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In 9 patients a correct diagnosis was undoubtedly missed, and they were treated by injection when ligation should have been performed as a preliminary step. Careful examination is necessary to determine the patency of the saphenofemoral valve in obese individuals where the saphenous vein may be buried deeply in fatty tissues. Trendelenburg and Schwartz tests may have to be repeated and correctly interpreted. Sometimes it will be necessary to palpate the saphenous in various locations of the thigh with the patient in different positions. In 3 patients the high ligation had to be supplemented by a ligation in a lower level of the thigh because of incompetency of the valve of the intercommunicating vein. This was demonstrated by the comparative tourniquet test.

One patient belonged to the Trendelenburg double positive group. Multiple ligations and injection treatment produced unsatisfactory results.

The remaining 34 patients showed a tendency to recurrence and reformation of superficial varicosities without any disturbance of the normal venous flow. These were treated periodically with sclerosing solution.

I have reviewed 132 patients of the second group who had recurrences following some form of ligation operation. High ligation in the saphenofemoral junction has been our operation of choice for many years. In earlier work, a few technically difficult cases were ligated in the upper third or middle of the thigh. The incision in the groin was also avoided in some obese individuals because of the presence of moist eczema. Seventeen such patients had recurrences and required high ligation.

I have discontinued performing ligation as a primary operation in the lower level. Experience has proved that the result in low ligation is unsatisfactory.

Since the publication of Edwards' important paper in 1934[1] regarding the anatomical pattern of the saphenous vein, many articles have appeared in the literature regarding the re-formation of venous channels through the uppermost tributaries of the saphenous. I have operated upon a few patients with recurrence of this type who had had their original operation elsewhere. In my own group I have encountered only 2 such cases. Both had had high saphenous ligations and were discharged after a satisfactory course of obliterative treatments. When next seen they were pregnant and suffering from marked varicosity of the labia. A few months after the termination of pregnancy one of these patients was reoperated upon, and with a great deal of difficulty I isolated a patent pudendal branch which had been missed during the original ligation. The second patient was successfully treated with only injection of sclerosing solution without further recurrence. Solomons[2] suggested injecting these pudendal varicosities during pregnancy with quinine and urethane. I have never had the courage to follow his suggestion. The patients I have seen with pudendal

varicosity during pregnancy almost always had an incompetent saphenofemoral valve complicating the condition, so I have advised them to wait for treatment until the termination of pregnancy.

The abnormal pattern of the uppermost part of the saphenous vein is common, and we have encountered a full share of various abnormalities. I have taken painstaking care to ligate any of the uppermost tributaries present. This is done routinely whenever the external pudendal, superficial circumflex, iliac, and superficial epigastric veins empty into the upper end of the saphenous vein instead of into the femoral vein. The accessory veins, lateral or medial femoral, are in the great majority of patients located too far distally to expose during high ligation. In some instances one of them may be located quite high and anterior to the saphenous and may be ligated by mistake as the saphenous vein. This was undoubtedly the cause of recurrence in a few patients I have exposed who had been operated upon elsewhere. Since we began routine peripheral injection of sclerosing solutions in the severed distal portion of the saphenous during ligation, we have encountered very few patent accessory femoral veins as the cause of recurrences. In the majority of patients this injection obliterates these accessory veins. In 6 instances it was found that patency of the accessory vein was the cause of recurrence. The lateral femoral vein was ligated and injected in 2 cases; by subsequent experience it was determined that by injection alone satisfactory obliteration could be obtained.

We have had limited experience in the past with the old stripping and excision operation. A few patients with recurrence and failure after such operation elsewhere responded satisfactorily to ligation and injection treatment in our service. We have also operated successfully upon 5 patients who have had the Schede type of operation elsewhere with failures.

Varicosities of the lesser saphenous almost always are caused by the pressure transmitted through communications with the long saphenous. In some of my earlier patients I ligated and excised the communicating vein just medially and behind the knee as a special precaution in addition to the high ligation. This additional step is very seldom necessary. High ligation of the saphenous and obliteration of the small saphenous alone will prove sufficient in the majority of patients. If the lesser saphenous is greatly dilated, it may have to be ligated in the popliteal space as described in previous publications.[3]

It has been my custom to remove a segment of the saphenous vein during ligation. Undoubtedly in some instances this procedure was not adhered to. I have never seen recurrences caused by reestablishment of ligated and cut ends. I have my honest doubts in this matter. In several instances during reoperation on patients operated upon elsewhere, a patent saphenous was found. This, I believe, was either missed during the original operation or ligated but not cut.

The great majority of recurrences in the ligated group in my own service occurred when there was not only an incompetency of the saphenofemoral valve but also of the one or more valves of the veins communicating between the deep and superficial systems of the thigh. Although familiar with this complication, it was not always possible to diagnose it or to differentiate it from the Trendelenburg double positive group.

To Ochsner and Mahorner[4] the credit is due for describing the comparative tourniquet test by which incompetency of the communicating veins in the thigh can be accurately demonstrated. They have also made it clear that this incompetency in the majority of patients is only limited to the thigh and fortunately does not extend below the knee. It can be easily understood that the normal flow of blood in the venous system of the lower extremities is from superficial to deep. But when incompetency of the valves of the intercommunicating veins is present, the blood flow is reversed from the deep to the superficial. Ninety-two patients with recurrences following high ligation required further ligation in one, two, or three lower levels in the thigh to produce a satisfactory result. These levels were determined by the simple comparative tourniquet test. In going over the record of these patients I found that in some the condition was not properly recognized, while in others it was not properly differentiated from the Trendelenburg double positive group. We also found another incipient group where the back flow through the saphenofemoral junction could be easily demonstrated, but the lower level of the leaks between the superficial and deep venous system could not be clearly determined until some time after high ligation was performed. For the last four years we have been performing the high and low ligations in one sitting in all indicated cases. I am convinced that this important step has helped in reducing the number of recurrences.

The remaining 15 unsuccessful cases belonged in the Trendelenburg double positive group and showed not only incompetency of the saphenofemoral junction and of the intercommunicating veins of the thigh, but also incompetency of the veins of the intercommunicating system in the calf and lower leg. Multiple ligations, excision, and segmental obliteration were performed. Though the immediate result proved satisfactory, the final follow-up was far from encouraging. Linton's[5] operation for the ligation of communicating veins in the lower leg may offer some hope to the patients who present multiplicity of symptoms caused by venous stasis. My own experience is limited to 2 such cases, and it is too early to draw any conclusions. This operation is of great magnitude and cannot be used as a routine measure. Uncomplicated cases belonging to this group could be made comfortable with a properly fitted elastic stocking or bandage. Fortunately, less than 2 per cent of varicose vein patients seen by us belonged to the Trendelenburg double positive group.

## CONCLUSIONS

1. When there is dilatation of superficial veins of the lower extremity without disturbance of the normal flow of the venous blood, adequate injection of sclerosing solution will prove satisfactory in the majority of patients.

2. If backflow of blood through an incompetent valve in the saphenofemoral junction is present, a high ligation and sectioning of saphenous followed by obliteration of varicosities will prove sufficient. Ligation of the uppermost tributaries of the saphenous when present and peripheral injection of the severed distal portion are valuable steps in the ligation operation.

3. Incompetency of one or more valves of the communicating veins of the thigh between the superficial and deep venous systems requires additional ligation in the lower level.

4. Multiple ligation, excision, and segmental obliteration in patients with incompetency of the valves of the communicating veins of the whole lower extremity including the calf and lower leg have not produced permanently satisfactory results. Linton's operation may offer hope in some patients. Uncomplicated cases can be made comfortable with elastic bandages.

5. Notwithstanding what method of treatment is used, there is a tendency in some patients to recurrence and re-formation of varicose veins. Observation of patients at regular intervals and critical investigation of the causes of recurrence and institution of proper treatment will decrease the number of failures.

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# BLOOD ETHER LEVELS IN SURGICAL ANESTHESIA

ROBERT POTTER, M.D., HUBERTA LIVINGSTONE, M.D., EDMUND ANDREWS, M.D., AND GERALDINE LIGHT, M.D., CHICAGO, ILL.

*(From the Department of Surgery of the University of Chicago)*

SINCE the first use of ether as a human anesthetic agent by Long in 1842, many determinations have been made in animals and a few in man to ascertain anesthetic and lethal levels. The problem has been approached mainly in two ways: (1) by measuring the ether vapor concentration in air, either as administered for anesthesia or as the alveolar tension when exhaled, and (2) by measuring the ether concentration in blood samples taken during anesthesia.

Probably the first determination of ether concentration in the anesthetic state was made in 1847 by Lassaigne,[1] who measured the ether in the venous blood of a dog. Since that time various workers including Snow,[2] Bert,[3] Madelung,[4] Stange,[5] Shaffer and Ronzoni,[6] Ronzoni,[7] Haggard,[8] Robbins,[9] and Calderone[10] have made determinations in animals by air analysis. Among those who have carried out ether determinations on blood samples from animals are Lassaigne,[1] Nicloux,[11] van Leeuwen,[12] Shaffer and Ronzoni,[6] Ronzoni,[7] Haggard,[13] Karber,[14] Robbins,[9] Calderone.[10] Determinations made by air analysis on human beings include those of Dreser,[15] Connell,[16] Boothby and Sandiford.[17] Direct determination of the concentration of ether in the blood of anesthetized human beings has been made by Gramen,[18] White,[19] Webb,[20] and Koller.[21] The interest of the workers cited above was variously distributed between anesthetic and lethal levels, distribution ratios, recovery curves, absorption and excretion, and possible synergism with other drugs.

The criteria for "surgical anesthesia" varied with the different workers. Muscular relaxation, loss of pain response, alteration of corneal or deep reflexes, character of respiration, etc., were considered among the criteria. However, in dogs at surgical anesthesia the results of Nicloux[11] (105 to 110 mg. per cent), of Haggard[13] (80 to 91 mg. per cent), of Robbins[9] (90 to 113 mg. per cent), and of Calderone[10] (81 to 95 mg. per cent), show good agreement and range only from 80 to 113 mg. per cent. Ronzoni[7] and van Leeuwen,[12] working with dogs and cats respectively, made more definite attempts to correlate anesthetic level with stage by determining loss of reflexes in response to electrical stimulation of nerve trunks.

Of more interest to us are the results in human beings. Gramen[18] made 700 determinations on 52 patients including expired air, urine, milk, and also venous blood, drawn at various times during or following operation. His monograph contains an excellent review of the literature on ether determinations. He considered five clinical stages of anesthesia with Stages III and IV being in the range of customary surgical anesthesia. He differentiated between Stages III and IV on

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the basis of pain reflexes from the operative field. For Stage IV, or deep surgical anesthesia, his results on 67 determinations ranged from 41 to 111 mg. per cent with an average of 80 mg. per cent. Koller[21] in 51 patients found a range of from 30 to 100 mg. per cent sufficient for surgical anesthesia. White[19] during de-etherization of 12 patients found that surgical anesthesia ranged from 100 to 150 mg. per cent while light surgical anesthesia varied from 70 to 100 mg. per cent.

There is apparent disagreement among the various workers as to the effect of morphine or morphine-scopolamine or other premedicant drugs on the blood ether levels required for surgical anesthesia. Madelung[4] found that one-half to two-thirds of the usual concentration of the anesthetic agent in the alveolar air of rabbits and dogs was sufficient for surgical anesthesia when morphine and scopolamine were given preoperatively.

Stange[5] reported that morphine lessened by one-third the concentration of ether necessary for light anesthesia in rabbits but did not lessen the dosage for deep anesthesia or respiratory failure, unless excessive doses of morphine were given. Calderone,[10] working with dogs, found that 2 to 5 mg. per kilogram of morphine did not lessen the concentration of ether in the blood necessary for either surgical anesthesia or respiratory failure. Barlow and Stormont[22] found that in rats, opium alkaloids are additive to nitrous oxide. Webb[20] found in human beings that venous blood following morphine 0.010 Gm. and atropine 0.0004 Gm. contained 41 to 110 mg. per cent of ether during light surgical anesthesia, and 110 to 170 mg. per cent during deep surgical anesthesia. Following an unstated amount of morphine and hyoscine he found blood ether levels ranging between 39 and 100 mg. per cent sufficient for abdominal operations.

In the above reports it should be noted that there is considerable difference in the amounts of the drugs employed. Stange and Madelung administered in rabbits 20 mg. per kilogram of morphine and 10 mg. per kilogram of morphine and of scopolamine respectively, while Calderone[10] used 2 to 5 mg. per kilogram of morphine in dogs.

It is the general belief among many surgeons and anesthetists that the preoperative administration of morphine alone or in combination with atropine or hyoscine materially reduces the amount of ether required to produce surgical anesthesia and shortens the induction time, in addition to quieting the unrest of the patient in anticipation of the operation and providing some analgesia immediately postoperatively. It is probable that this concept has developed from clinical observation and does not represent controlled investigation.

In this study we have attempted to evaluate the effect of morphine alone, or in combination with hyoscine or atropine on ether levels in surgical anesthesia. With a simple, rapid method for determining blood ether concentration at our disposal,[23] determinations were made on patients using various methods of administration of ether anesthesia both with and without premedication. Special emphasis was placed

on bringing the patients to the same level of anesthesia as determined by the clinical signs described by Guedel.[24] The various groups were compared in an attempt to evaluate the effect of premedication on the concentration of ether in the blood.

### ANESTHETIC METHODS AND PREMEDICATION

Consecutive patients receiving ether anesthesia were used in this study. They included neurosurgical, upper and lower abdominal, plastic and tonsil cases. The ages varied from 5 to 70 years.

Premedication consisted of morphine alone, morphine-atropine, or morphine-hyoscine, and codeine in the case of young children. These drugs were administered in the usual clinical doses of 0.010 to 0.015 Gm. of morphine, and 0.0003 to 0.0004 Gm. of atropine or hyoscine. Codeine ranged from 0.02 to 0.03 Gm. In every case the premedication was administered twenty to forty-five minutes before the induction of the anesthetic. A small series received avertin as basal anesthetic, and some patients received no premedication.

Four different anesthetic methods were employed: (1) induction and maintenance with open-drop ether on a Schimmelbusch face mask, designated as "drop alone"; (2) short semiopen induction with nitrous oxide-oxygen for two to five minutes, followed by open-drop ether on a Schimmelbusch face mask, designated as "nitrous oxide-oxygen to drop"; (3) short semiopen induction with nitrous oxide-oxygen followed by a closed system with ether dropping in a rebreathing bag; there was maintenance flow of oxygen, and soda lime absorption of carbon dioxide, designated as "closed metric"; (4) semiopen induction with nitrous oxide-oxygen, followed by constant flow of nitrous oxide and oxygen over ether, designated as a "semiopen $N_2O$-$O_2$ constant flow with ether." Ethylene could not be used as an induction agent as it appeared in the blood samples, and was found to be present, although not quantitatively, in the analysis.

### ANESTHETIC LEVEL AND THE BLOOD SAMPLE

The selection of a standard level of anesthesia in an assay such as this is extremely difficult. So-called "surgical anesthesia" will show a wide range of variability. Ronzoni[7] suggested also that the length of time under anesthesia is a factor in the amount of ether required. Gramen[18] used the abolition of pain in human beings as the criterion but showed that this varied between cutaneous, muscular, and peritoneal stimulation. Others have employed electrical stimulation of nerves and reflexes in an attempt to set levels of anesthesia.

In this work we attempted to use the signs regularly employed in anesthesia, both because they represented a convenient and commonly accepted method and because of the greater familiarity of the anesthetists with these signs. Muscular relaxation, character of respiration, eye signs, and absence of superficial reflexes, as defined by Guedel,[24] were employed as criteria of the depth of anesthesia. All blood samples were drawn at the second plane of the third or surgical

stage of anesthesia. These were taken after the induction and before the operation was begun and after careful selection of the anesthetic stage by one of three experienced anesthetists. The subsequent course of the anesthetic was checked, and in cases where it was apparent that the stage had been incorrectly designated, the samples were rejected.

Single samples of blood were collected in 2 c.c. precision syringes which were found to have an error of only 0.5 to 2 per cent. Occasionally duplicate samples were run and the results were always within the limit of error of the technique. The blood samples were analyzed for ether content by a modified dichromate-sulfuric acid method recently described by some of us.[23] With this technique 97 to 101 per cent of ether was recovered from standard solutions of water and of blood containing ether.

The blood was necessarily drawn from the venous system, the large veins of the arm being employed. It is evident that heart, arterial, or internal jugular puncture is barred as a routine for patients. Haggard[13] aptly points out that unless the organism is at equilibrium or in the process of elimination of ether with moderate breathing, a venous sample from the extremity is not indicative of ether saturation for purposes of determining physiologic response. However, because the samples were always taken under comparable conditions, after smooth inductions and at apparently the same stage of anesthesia, and because the ether administration was stopped during the time of determination of the stage and drawing of the sample, it is fair to state that the samples are of clinical value, and if not representing a state of equilibrium, at least are close to it.

To check the accuracy of this contention, two blood samples were taken from each of 10 patients that were examined in the following manner. The first blood sample was drawn at the second plane of the third stage. The anesthetic was then deepened to the early fourth stage and stopped, allowing the patient to return to the second plane of the third stage by de-etherization. At this time a second blood sample was drawn. The data from this study appear in Table I. It is interesting to observe that the variation is about equal on either side, and that the second sample was slightly higher in 4 cases and slightly lower in 6 cases. It is obvious that this process of prolonged de-etherization from deep anesthesia cannot be employed routinely in human subjects for a large series of cases.

## RESULTS

Simple averages do not show as much as graphic presentation, and the best method of analysis is statistical comparison as employed in biologic drug assays. Our data were submitted to a competent statistician* for statistical analysis by the method of Fisher.[25]

For purposes of analysis the data were considered (1) under the different categories as determined by various methods of anesthesia

*We are indebted to Dr. Bert Vos for the statistical analysis presented.

TABLE I

| CASE NO. | BEFORE DEEP SATURATION (MG. %) | AFTER DEEP SATURATION (MG. %) |
|---|---|---|
| 1 | 61 | 70 |
| 7 | 65 | 75 |
| 9 | 75 | 85 |
| 10 | 75 | 84 |
| 2 | 69 | 49 |
| 3 | 71 | 70 |
| 4 | 88 | 82 |
| 5 | 113 | 86 |
| 6 | 113 | 73 |
| 8 | 101 | 95 |

and various combinations of premedication used, and (2) under the combined groupings with and without premedication. The amount of ether used, the time consumed by the induction, the simple averages of blood ether levels, and the ranges covered in each category appear in Table II. In collecting the data for "combined" comparison, only the anesthetic methods of "drop alone," "nitrous oxide-oxygen to drop," and "closed metric" could be used, since the effect of nitrous oxide was in force in "semiopen nitrous oxide-oxygen constant flow with ether" as the ether levels of this category indicate. As far as the effect of nitrous oxide used only for early induction is concerned, this nitrous oxide was probably in greater part eliminated from the system during the subsequent period of ether administration. Kemp[26] cites a single instance where the nitrous-oxide level in the venous blood of a dog fell from over 20 per cent, an anesthetic level, to 6.9 per cent in

TABLE II

| | AMOUNT ETHER USED (AVERAGE) | TIME (AVERAGE) (MIN.) | AVERAGE (MG. %) | LIMITS (MG. %) | NO. OF CASES |
|---|---|---|---|---|---|
| Drop alone | | | | | |
| No premedication | 3.3 oz. | 12 | 93 | 61-117 | 34 |
| After morphine | 4 | 16 | 113 | 73-136 | 9 |
| Nitrous oxide-oxygen to drop | | | | | |
| No premedication | 4 oz. | 12 | 93 | 62-130 | 44 |
| After morphine | 5 | 13 | 95 | 77-149 | 10 |
| Closed metric | | | | | |
| No premedication | 27 c.c. | 12 | 90 | 59-129 | 26 |
| After morphine-hyoscine | 33 | 13 | 87 | 52-131 | 25 |
| After morphine-atropine | 29 | 13 | 89 | 75-116 | 6 |
| After morphine alone | 26 | 14 | 89 | 52-127 | 15 |
| Combined after premedication | 29.6 | 13.7 | 88 | 52-131 | 46 |
| Semiopen nitrous oxide-oxygen constant flow with ether | | | | | |
| No premedication | 2 oz. | 17 | 59 | 25-103 | 14 |
| After premedication | 2 | 14 | 70 | 26-131 | 18 |
| Combined comparison: drop alone, nitrous oxide-oxygen to drop, and closed metric | | | | | |
| No premedication | | | 92 | 59-130 | 104 |
| After premedication | | | 92 | 52-149 | 65 |

less than two minutes. It is a common clinical observation that recovery of consciousness from nitrous oxide-oxygen anesthesia takes place almost immediately after the anesthetic is discontinued. In substantiation of this belief we note that graphic comparison of the "drop

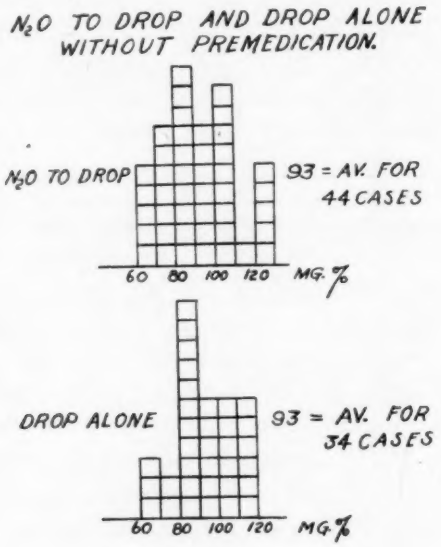
$N_2O$ TO DROP AND DROP ALONE WITHOUT PREMEDICATION.
$N_2O$ TO DROP
93 = AV. FOR 44 CASES
60 80 100 120 MG. %
DROP ALONE
93 = AV. FOR 34 CASES
60 80 100 120 MG. %

Fig. 1.

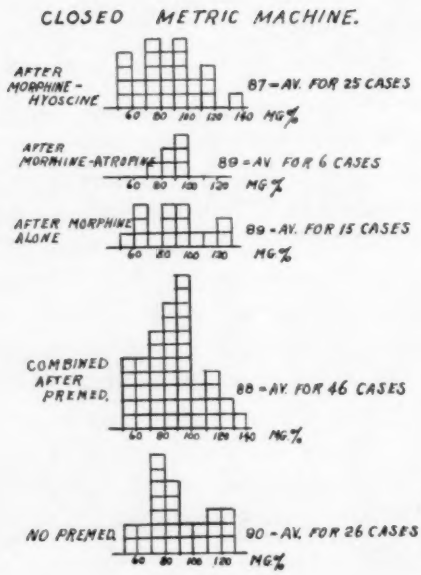


Fig. 2.

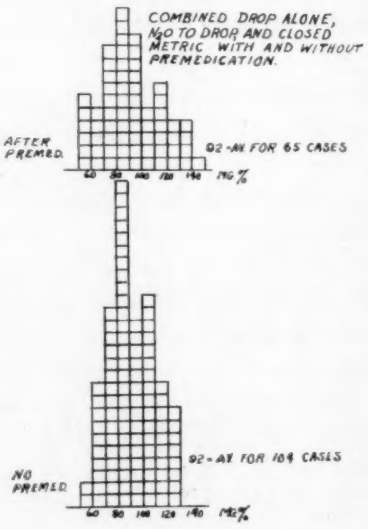
COMBINED DROP ALONE, $N_2O$ TO DROP AND CLOSED METRIC WITH AND WITHOUT PREMEDICATION.
AFTER PREMED.
92 - AV. FOR 65 CASES
NO PREMED.
92 - AV. FOR 109 CASES
MG %

Fig. 3.

alone" and "nitrous oxide-oxygen to drop" both without premedication show similar distribution (Fig. 1) and by statistical analysis by Fisher's method shows no significant difference between the series ($P = 0.8$).

The graphical presentation of the various types of premedication with the "closed metric" method of anesthesia appears in Fig. 2.

Statistical study of the "closed metric" method, comparing 26 cases with no premedication with (a) 25 cases with morphine-hyoscine and (b) 46 combined cases with premedication, gives P values of 0.5 and 0.9 respectively which represent no significant differences between the series compared. Fig. 3 is a graphic representation of the results in the combined categories of "drop alone," "nitrous oxide-oxygen tc drop," and "closed metric," comparing those with and those without premedication. The statistical comparison of the combined groups gives P = 0.1, which indicates no significant difference between the series.*

It should be mentioned that 6 cases were run with avertin as a basal anesthetic supplemented with drop ether. Eighty to 95 mg. per kilogram of avertin were used, and an average of three to four ounces of ether, the average time of induction being twelve minutes. The blood ether levels showed widespread variations; i.e., 60, 70, 60, 110, 125, and 28 mg. per cent for the 6 cases.

## COMMENT

In evaluating data of this type, the limitations of the method must be kept clearly in mind. An investigative problem such as this is greatly complicated by the difficulties in the clinical determination of the anesthetic stage, the individual variation in reaction to the premedication and the anesthetic agent, and the variations in the general condition of patients encountered in routine surgery. Thus a large series must be studied the better to evaluate these variables.

From this series a number of observations may be made. The premedication used had little effect on the time required for the production of surgical anesthesia or on the amount of ether used. Certainly the medication did not markedly shorten the induction period; in fact, there was a slight increase in the induction time which is in agreement with Flagg,[28] who stated that morphine and atropine as preliminary medication prolong the induction with the open method. It is apparent from Fig. 3 that there was a wider divergence in blood ether levels in the presence of premedication. This is probably due in part to the obscuring of some of the anesthetic signs, since more difficulty was experienced in determining exactly the anesthetic stage after premedication. It is interesting to note that Gwathmey[29] states that the administration of morphine and scopolamine before colonic ether-oil makes the pupillary signs of little value.

From these results it is apparent that by our method there is no observable difference in blood ether levels between the groups receiving morphine, morphine-atropine, or morphine-hyoscine and the groups receiving no premedication. This observation is apparently at variance with the results of Madelung and Stange in their work with rabbits and of Webb in determinations on human beings. Although it is difficult to

*The combined categories were analyzed by the method of Yates and Brandt as given by Snedecor.[27]

translate quantitatively the effect of depressant drugs from rabbits to human beings, it is probable that the amounts employed by Madelung and Stange of 10 and 20 mg. per kilogram of morphine are much greater than the usual dosages employed in human beings. Our observations are in accord with those of Calderone who found that dosages of 2 to 5 mg. per kilogram of morphine had no effect on the ether levels required for surgical anesthesia.

It is interesting to note that our series falls in fair approximation with other determinations of surgical anesthesia. The limits ranging from 59 to 139 mg. per cent, with an average of 92 mg. per cent, is about 12 mg. per cent above that of Gramen who had a large and carefully controlled series and whose stage designated as Stage IV loosely approximated our standard level. It is difficult, however, to compare series in which varying criteria were selected for determination of anesthetic level.

In conclusion we wish to state that this work has been an attempt to determine if the preanesthetic use of morphine, morphine-atropine, or morphine-hyoscine in the usual clinical doses affects the blood ether concentration necessary to produce surgical anesthesia. We do not wish, however, to discredit the use of these and other kinds of premedication, as they have a very definite selective use in preoperative preparation. Their role in decreasing apprehension, their synergistic action with gas anesthesia making it possible in indicated cases to avoid the use of ether, makes them very valuable adjuncts to anesthesia.

## SUMMARY

1. The results of blood ether determinations on 207 clinical patients with various methods of anesthesia, with or without premedication, are presented.

2. Comparison by graphic and statistical methods reveals that patients without premedication, or with commonly used premedication, show no significant variation in blood ether levels at the second plane of third stage anesthesia.

3. Morphine in the dosages commonly employed does not appreciably decrease the time of, nor increase the ease of, induction with ether and often obscures the signs of anesthesia so that frequently higher ether levels are found after its use.

4. Blood ether levels without premedication at the second plane of the third stage of anesthesia vary from 50 to 130 mg. per cent, the greatest number falling between 80 and 100 mg. per cent.

We wish to thank Dr. T. E. Friedemann, Dr. B. F. Vos, Dr. R. Engel, and Dr. C. Vermeulen, and Mr. L. Hrdina, as well as the members of the anesthesia department, for their assistance in this study. We also wish to express our appreciation of the cooperation given us by the surgeons who made this investigation possible.

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# A COMPLICATION FROM THE USE OF GLOVE POWDER

FRANCIS X. BYRON, M.D., AND C. STUART WELCH, M.D.
ALBANY, N. Y.

*(From the Departments of Pathology and of Surgery, Albany Medical College, Union University, and the Albany Hospital)*

NODULES in operative scars sometimes present interesting problems in diagnosis. Commonly, they are due to malignant implants or metastases or to foreign bodies, such as suture material and cotton threads. In some cases tuberculosis and endometriosis are found. In this communication we wish to call attention to the importance of talcum powder as a causative agent not only of nodules in the skin and subcutaneous tissue of abdominal incisions, but also of tubercle-like lesions on the peritoneum. During the last year we have seen several cases in which talcum powder was responsible for the development of these lesions. Not infrequently the nodules it produces are tender to palpation and may even be painful. In the cases which we have observed, small nodules consisting of miliary granulomatous lesions resembling tubercles have been found in old abdominal incisions in 3 cases and on the peritoneal surface in 2 cases in which multiple abdominal operations had been performed. A brief report of 4 typical cases with the pathologic findings follows.

## CASE REPORTS

CASE 1.—A negress, 51 years of age, presented herself at the Outpatient Department of the Albany Hospital with the complaint of pain in the region of an old operative scar in the low midline of her abdomen which had been present for one week. Five years before she had had an abdominal hysterectomy and bilateral salpingo-oophorectomy for multiple leiomyomas. Examination of the old incision revealed a hard, immobile, tender mass approximately 2.5 cm. by 4 cm. in size. The blood Wassermann reaction was four plus. A tuberculin test was read as two plus. There was evidence of healed primary tuberculosis on roentgenologic examination of the chest. Biopsy of the lesion was taken. Grossly the tissue appeared yellowish white in color and was firm to palpation. Microscopically many small discrete and conglomerate foreign body granulomas showing a central framework of epitheloid cells, a surrounding zone of multinucleated giant cells and lymphocytes, and a peripheral fibrous tissue reaction were seen. The lesions were considered to be miliary tubercles in the scar tissue of the abdominal wall. Examination of the tissue under the microscope with polarized light was suggested after our attention was called to the work of Fienberg[1] on the subject of talcum granuloma. Fig. 1*A* is a photomicrograph of the tissue removed from the abdominal incision of this patient. Typical miliary tubercles can be seen in the section. Fig. 1*B* is a photomicrograph of the same area taken after polarization of the light to demonstrate the talcum. The crystalline deposits can be seen in the foreign body giant cells.

CASE 2.—The second case is one in which tubercles of talcum powder origin were found on the peritoneal surface of the ileum removed from a 23-year-old man with regional ileitis. Before resection of the ileum and right colon was performed, two previous operations had been done. He had first been operated upon elsewhere for

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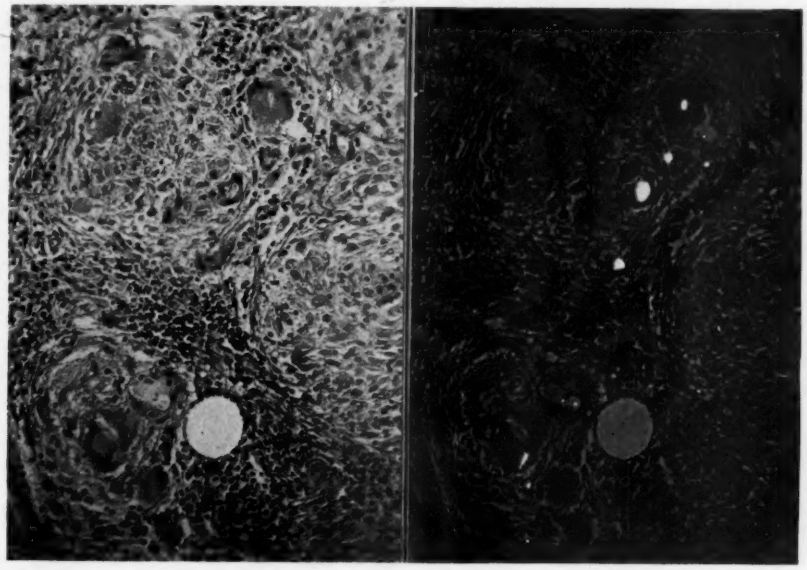
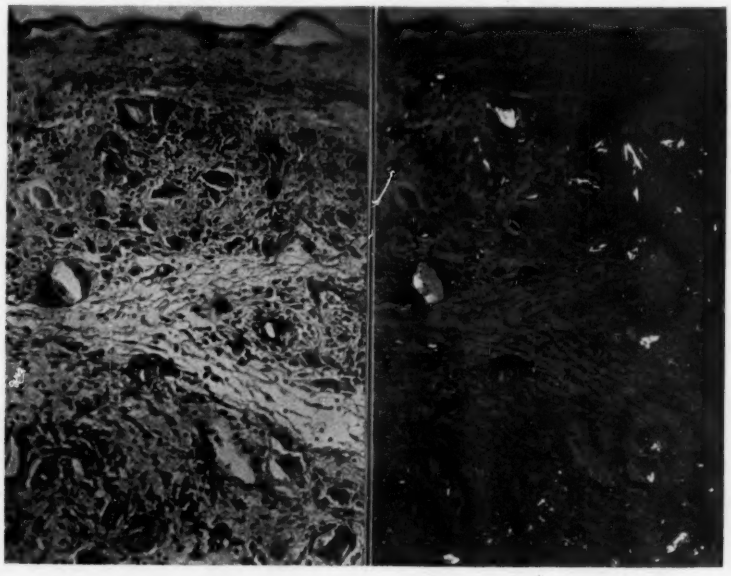
what seemed to be acute appendicitis. He had also had an ileocolostomy performed at the Albany Hospital as a first-stage operation preliminary to resection. Microscopic examination of the peritoneal surface of the ileum revealed multiple tubercles, which upon examination under polarized light, proved to contain crystals which were undoubtedly talcum powder. In Fig. 2*A* and *B* an area from the markedly thickened serosa of the ileum is shown. In Fig. 2*B* the crystalline deposits are visible under polarized light.



*A.* *B.*

Fig. 1*A*.—Photomicrograph of foreign body giant cells containing talc crystals in tissue removed from abdominal scar in Case 1. *B*, Same section as shown in *A* photographed after polarization of light.

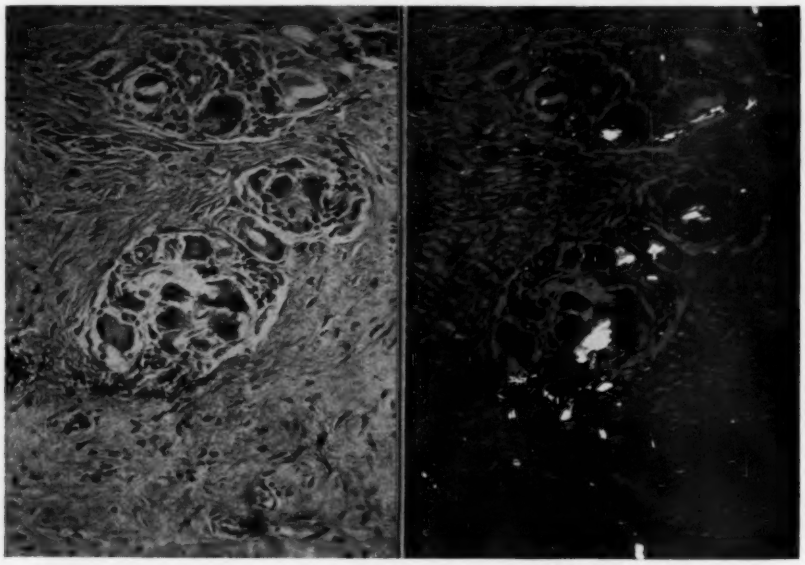


*A.* *B.*

Fig. 2*A*.—Photomicrograph of crystals of talc and foreign body giant cells on serosal surface of ileum in case of ileitis (Case 2). *B*, Same as shown in *A* photographed with polarized light.

CASE 3.—In the third case, a man upon whom suprapubic cystostomy had been performed, the microscopic picture was identical, and in Fig. 3*A* and *B* one can see again under ordinary light (Fig. 3*A*) and under polarized light (Fig. 3*B*) the microscopic findings in a section taken from a painful nodule in an old low midline incision.

CASE 4.—In the fourth case there were talcum powder granulomatous lesions both in the abdominal incision and upon the peritoneal surface of the intestine. The patient was a woman, 31 years of age, upon whom a panhysterectomy and bilateral salpingo-oophorectomy had been performed two months previously for papillary cystadenocarcinoma of the ovary. Three weeks after her original operation a secondary laparotomy had been performed for the relief of intestinal obstruction which developed during the postoperative period. The patient was admitted to the hospital some two months after her first operation because of a tender mass in the abdominal incision, the site of a previous enterostomy. Examination of this mass after removal showed it to be a foreign body granuloma, probably due to glove powder. At a later operation for intestinal obstruction the patient died from cyclopropane poisoning. At autopsy only one nest of cancer cells implanted upon the peritoneum of the ileum was seen. There was, however, an area of inflammatory reaction about the terminal ileum. Microscopic examination of the surface of the ileum in this region showed multiple tubercle-like structures in which foreign body giant cells containing a crystalline material similar to that seen in the lesions described.



*A.* *B.*

Fig. 3*A*.—Section from tissue removed in Case 3. The crystalline deposits and the foreign body giant cells were abundant. *B*, Photograph of same tissue as shown in *A* after polarization of light.

## COMMENT

Surgical powder usually consists of magnesium silicate or talc, although lycopodium spores are sometimes used. The reaction of the body to the presence of lycopodium spores is quite similar, except for the fact that the spores, which are larger than crystals and are organized vegetable cells, are usually clearly visible in the lesions. Apparently, however, the lycopodium powder causes a higher percentage of reactions than does talc. Sinus tract formation is more liable to occur. Experi-

mental evidence would seem to indicate that the tissue reaction to talc is due to a chemical irritation.[4] That the reaction to lycopodium may also be due to a chemical factor is pointed out by Erb,[2] who calls attention to the fact that the spores are acid-fast just as are tubercle bacilli and that the lesions produced are almost identical.

Fienberg has reported several cases in which talc seems undoubtedly to be the etiologic agent. Antopol[3] has reported additional cases in which lycopodium was the agent responsible for a similar tissue reaction. Erb has reviewed the literature on lycopodium and added his experiences with some of these granulomatous lesions.

While the lesions histologically resemble those of tuberculosis, yet in none of them could *Mycobaterium tuberculosis* be found in preparations stained by Ziehl-Neelsen technique. A geologist whom we consulted believed that the crystals were undoubtedly talc, since crystals of other substances which resemble talc are not used in surgery. The crystals seen in the tissue examined by us belonged to the monoclinic system with extinction angles corresponding to those of magnesium silicate. We have reviewed sections in cases of known tuberculosis of the soft tissue and in none of these have crystals and amorphous material been seen.

The finding of talcum powder in pseudotubercles on the peritoneum in 1 case of regional ileitis and in another in which multiple abdominal operations had been performed was most interesting to us. The possibility of implanting talcum in cases of regional ileitis is enhanced because of the fact that multiple operations before resection are not uncommon, and also because the serosal surface of the intestine is injured by inflammation. In the reported Case 2 an operation for appendicitis had been done elsewhere, and after coming under our care, a preliminary ileocolostomy was done making two inoculations with powder probable. In none of the descriptions of ileitis have we found talcum mentioned as an agent which may be responsible for part of the pathologic picture. In spite of the fact that glove powder is responsible for these surgical complications, its advantages over the older wet glove technique are too great, in our opinion, to recommend a change to the latter. We would recommend that gloves be carefully washed in the hand basin after they are put on in order to eliminate as much powder as possible. Furthermore, a minimum of powder should be used both in the preparation of gloves and in the preparation of the hands. To be aware of this complication resulting from the use of glove powder and to avoid confusion in the diagnosis of nodules in abdominal incisions are the particular aspects of this subject which we wish to stress.

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# A TECHNIQUE FOR THE MEASUREMENT OF LOCAL FLUID LOSS IN EXPERIMENTAL TRAUMATIC SHOCK

M. L. Cullen, M.D., and N. E. Freeman, M.D., Philadelphia, Pa.

*(From the Harrison Department of Surgical Research Schools of Medicine, University of Pennsylvania)*

IN THE course of experiments on traumatic shock, it became necessary to measure the amount of fluid lost into the traumatized extremities. The present experiments were undertaken to test the accuracy of measuring fluid loss by careful anatomical separation of the homolateral extremities with intervening tissue and comparing the weights of opposite sides.

## TECHNIQUE

After clipping the hair from the areas to be incised, with the dog placed on its abdomen, a midline incision was made from just below the base of the skull down over the middle of the spine to the tail. From the caudal end of this incision two oblique symmetrical incisions were made on either side of the tail and rectum. The superficial fascia and attachments of trapezius and latissimus dorsi muscles were divided close to the spinous processes. The origins of the latissimus dorsi were cleanly separated from the lumbodorsal fascia and the last two ribs. The erector spinal muscles were left on the trunk.

With the knife edge kept close to the pelvic bone, the mass of hip muscles was dissected from the external surface of the pelvis, and the muscles emerging from the pelvis were cut at their points of exit, except that the psoas muscles were cut at their insertions on the femurs. The capsules of hip joints were cut.

The dog was then placed on its back and a midline incision was made from the neck to the caudal end, from which point this incision was forked so as to pass around the external genitals to meet the dorsal oblique incisions. In the thoracic region the incision was extended down to the middle of the sternum and the pectoralis muscles were dissected from the chest wall. Care was taken to leave the attachments of the recti and external oblique muscles intact. In the region of the abdomen the skin and all the superficial fat and fascia were reflected from the abdominal muscles.

Skin and fascia were then dissected from the muscles of the neck laterally to the jugular vein. The subclavian vessels and brachial plexus were exposed. The vessels were ligated and divided. The in-

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sertions of the rhomboids and serratus muscles were dissected from the vertebral border of the scapula, and these muscles were separated from the latissimus dorsi and were not included with the extremities. The skin, omotransverse and brachiocephalic muscles were cut across just below the ascending cervical branch of the jugular vein and just above a group of lymph glands present in this region. The upper extremity was thus severed from the trunk.

The femoral vessels were exposed, cut, and ligated. The external genitals were removed from the pubis and the origins of the adductor muscles in the midline of the pubis were divided down to the symphysis. The muscles attached anteriorly to the external surface of the pelvis were freed from the bone, and the posterior extremity was thus severed from the trunk.

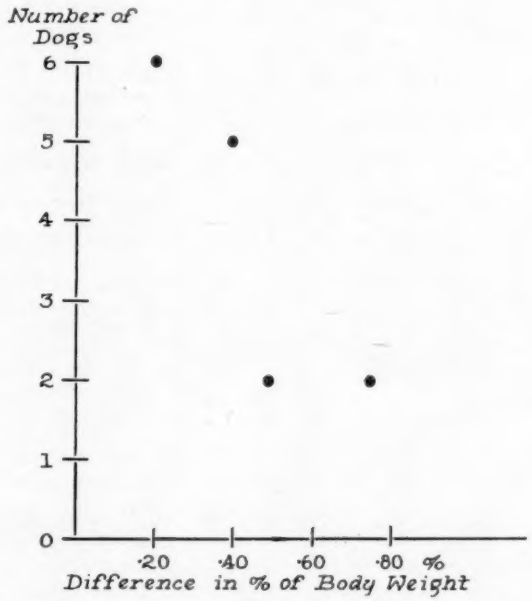


Fig. 1.

In this manner both extremities with superficial tissues of the trunk on each side were removed in one piece. Such dissection included fluid which had extravasated into the groins and flanks. The paired extremities of either side were weighed on a scale with an accuracy of 1 Gm., and these weights together with the total weight of the dog were recorded. The dissection and weighing were readily accomplished within an hour's time.

Fifteen control dissections and 6 dissections on traumatized dogs were performed. In 2 of the controls (Nos. 9 and 10) the method was further tested by injecting a known weight of blood into the extremities on one side. The amount of weight "recovered" was then compared to that injected.

In the traumatized experiments, trauma was performed by the technique of Kendrick, Essex, and Helmholz.[10] The dogs were anesthetized with ether and 1,500 blows with a rubber hammer were administered over a forty-minute period to both the fore- and hindmuscles on one side.

TABLE I

CONTROL DISSECTION EXPERIMENTS

| EXPERIMENT | WEIGHT (GM.) | | | | FLUID LOSS AS PER CENT OF BODY WEIGHT | REMARKS |
|---|---|---|---|---|---|---|
| | TOTAL WEIGHT OF DOG | LEFT EXTREMITIES | RIGHT EXTREMITIES | DIFFERENCE | | |
| 1 | 15,000 | 2,745 | 2,730 | 15 | 0.10 | Normal male accidentally killed under ether |
| 2 | 9,700 | 1,770 | 1,820 | 50 | 0.51 | Postoperative death (bilateral abdominal sympathectomy); previous thoracic sympathectomy |
| 3 | 5,400 | 970 | 975 | 5 | 0.09 | Postoperative death (bilateral stellate ganglionectomy and abdominal sympathectomy) |
| 4 | 5,000 | 860 | 866 | 6 | 0.12 | Same circumstances as in No. 3 |
| 5 | 6,000 | 1,168 | 1,139 | 29 | 0.48 | Same circumstances as in No. 3 |
| 6 | 5,300 | 562 | 574 | 14 | 0.26 | Same circumstances as in No. 3 |
| 7 | 10,500 | 2,330 | 2,296 | 34 | 0.32 | Died 2 days after severe bleeding; moderate hematoma in right thigh; obese |
| 8 | 13,500 | 1,645 | 1,700 | 55 | 0.40 | Killed by chloroform; lying on right side several hours before dissection |
| 9 | 5,700 | 883* | 880 | 3 | 0.05 | Tested for recovery of blood injected into thigh muscle |
| 10 | 5,400 | 850† | 810 | 40 | 0.74 | Died from peritonitis; tested as in No. 9, but there was leakage of injected blood before the weighing was done |
| 11 | 13,600 | 2,815 | 2,710 | 105 | 0.77 | Lying on left side many hours before dissection; fur on this side wet |
| 12 | 17,400 | 3,155 | 3,200 | 45 | 0.20 | Normal male accidentally killed under ether |
| 13 | 5,000 | 523 | 538 | 15 | 0.30 | Died 10 days postoperatively of distemper and pneumonia |
| 14 | 5,300 | 625 | 636 | 11 | 0.20 | Died 3 wk. postoperatively; pneumonia and pleural effusion |
| 15 | 14,900 | 1,999 | 1,942 | 57 | 0.38 | Died 24 hr. postoperatively; massive consolidation of right lung |
| Average | | | | 32.2 | 0.32 | |

*Total weight of this extremity at dissection was 1,133 Gm. minus 250 Gm. injected for testing recovery equals 883 Gm.

†Total weight of this extremity at dissection was 1,110 Gm. minus 340 Gm. injected for testing recovery equals 850 Gm.

## RESULTS

In 15 control dissections (Table I) an average difference with respect to body weight of 0.32 per cent was obtained. In 1 case (No. 10) a larger error resulted when the bisected part, which had been injected with blood, was allowed to rest in a pail, and there was leakage of some of the injected blood. In another case (No. 11) a larger error resulted possibly because the skin of one side was wet before the dissection. Excluding these errors, the control figures might have been lowered. Fig. 1 shows the distribution of difference in weight between the two sides expressed in terms of body weight. In 11 out of 15 control dissections, the difference was less than 0.4 per cent.

TABLE II

LOCAL FLUID LOSS IN TRAUMATIZED DOGS*

| EXPERIMENT | WEIGHT (GM.) | | | | FLUID LOSS AS PER CENT OF BODY WEIGHT | REMARKS |
|---|---|---|---|---|---|---|
| | TOTAL WEIGHT OF DOG | TRAUMATIZED EXTREMITIES | NORMAL EXTREMITIES | DIFFERENCE | | |
| 1 | 17,000 | 4,705 | 3,835 | 870 | 5.1 | Recovered from trauma; sacrificed 7 hr. later; autopsy showed only signs of hemorrhage |
| 2 | 13,900 | 3,400 | 2,800 | 600 | 4.3 | Died 1 hr. after trauma in shock |
| 3 | 7,200 | 1,780 | 1,410 | 370 | 5.1 | Died 3 hr. after trauma in shock |
| 4 | 12,700 | 2,825 | 2,340 | 485 | 3.7 | Died 3½ hr. after trauma in shock |
| 5 | 11,000 | 1,920 | 1,615 | 305 | 3.5 | Died 4 hr. after trauma in shock |
| 6 | 6,000 | 1,305 | 957 | 348 | 5.8 | Died in shock 3½ hr. after trauma; previously partially sympathectomized, but left splanchnics were intact |

*Average difference, 496.3 Gm.; average per cent loss in regard to body weight, 4.6.

In 6 dissections on traumatized dogs (Table II), an average difference of 4.6 per cent with respect to body weight was obtained. These figures approximate the figures on local fluid loss in comparable experiments by Blalock and others. In absolute figures there was an average "dissection" error of 32.3 Gm. in controls compared to an average difference of 496.3 Gm. in the dissections on traumatized dogs.

## DISCUSSION

Cannon and Bayliss[1] first attempted to measure local fluid loss in experimental traumatic shock by amputating the legs with symmetrical cuts across the upper thighs and comparing the weight of the traumatized leg with that of the opposite normal leg. It was later shown by Parsons and Phemister[2] and Blalock[3] that such measurements failed to include blood and fluid which extravasated into the groin and flank. Blalock modified their technique by making a midline abdominal incision, tying off the aorta and vena cava, clamping the iliac vessels,

splitting the symphysis pubis with a saw, removing the rectum and bladder, and bisecting the carcass in the midabdominal region. He then divided the hind end of the animal by sawing down the middle of the vertebral column. In a later article Blalock[4] described another method for measuring local fluid loss in experimental burns. This technique consisted in removing all abdominal and thoracic contents, sawing off the head in the plane of symmetrical transverse cervical incisions, sawing through the symphysis pubis, and removing the vertebral column and tail en masse by sawing across all the costovertebral junctions and the sacroiliac joints. The animal was thus bisected. No control figures were given to show the accuracy of this method. More recently Harkins,[5] using Blalock's second technique, gives the results on bisections of 7 normal animals. He found an average difference between the two sides equivalent to 0.38 per cent of body weight. Harkins has also devised a method (Nos. 6 and 7) for measuring fluid shifts continuously in experimental burns by the use of a "tipping" apparatus. While this technique is useful in studying the time of weight increase in the case of burns, it does not appear to be practicable in trauma experiments. Best and Solandt[8] are at present measuring local fluid loss after trauma by means of displacement of water. They then dissect out any tissue in the groin and flank containing blood which has collected there and add it to the weight of the limb. A detailed description of this work has not yet appeared in the literature.

The method described in this paper of measuring local fluid loss by anatomical dissection is not without error, but the error is small in comparison to the difference in weight observed in "trauma" experiments. The error is theoretically less than that occurring in the use of Blalock's bisection technique, since less tissue unaffected by trauma is included. In addition, the use of simple dissection appears to have the advantage of speed over the necessity for using a saw, as in Blalock's method.

With practice in the dissection the error can be made still lower. The results in the last 4 dissections (the figures are listed chronologically) indicate a smaller error, 0.27 per cent, than in those of the earlier dissections.

The use of comparative weights of normal and traumatized limbs as a measure of local fluid loss has been criticized[9] on the grounds that a large portion of the fluid in the traumatized area comes from the normal side, thus doubling the error. This argument appears to be fallacious in view of the fact that the extravasated fluid in the area of trauma comes from the rest of the body as well as from the normal extremities.

## SUMMARY

A method is described for the measurement of local fluid loss in experimental traumatic shock.

In 15 control experiments an average error equivalent to 0.32 per cent of body weight was obtained.

In 6 trauma experiments there was an average local fluid loss equivalent to 4.6 per cent of body weight.

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# CAJEDROL

## A New Analgesic and Antiseptic for the Genitourinary System

Charles F. Elvers and Carl E. Burkland, Baltimore, Md.
*(From the James Buchanan Brady Urological Institute, Johns Hopkins Hospital)*

SEVERAL years ago one of us (C. F. E.) noted that among the many patients treated at the Brady Urological Institute for interstitial cystitis, tuberculosis of the bladder, tumors of the bladder, etc., a small percentage obtained considerable relief from their acute symptoms, as well as from the discomfort following fulguration and instrumentation, if a small quantity of oil of niaouli was injected into the bladder immediately after the treatment was given.

Although this was effective in many cases, the results were not all that could be desired and a number of patients were found who did not react favorably to the niaouli.

In the preparation used, the active principle consisting of oil of niaouli is carried in a medium of olive oil, the viscosity of which makes its injection into the bladder difficult unless a special pelvic syringe of fairly large caliber is used. It was available in the United States as a proprietary product only, the supply then being limited, and at present being rather difficult to obtain.

Because of the results obtained in favorable cases following the instillation of this solution, it seemed highly desirable that a preparation be produced which would contain all of the elements of medicinal value found in niaouli oil, and in addition, be more highly bacteriostatic, nonirritating, and of a viscosity which would permit its being easily injected through catheters or instruments of small caliber.

A survey of the list of products derived from numerous plants of the Myrtaceae family and particularly the species Melaleuca, the group from which niaouli oil is obtained, revealed an interesting group of oils containing alcohols, aldehydes, terpenes, etc., of considerable medicinal value, most of which have been in general use in the Orient for centuries and some of which are now recognized and described in the materia medica of Europe and America.

Among this group of oils one was found which seemed to possess practically all of the desirable features for which we were seeking. This was cajeput oil, the essential oil extracted by distillation from the fresh leaves and twigs of *Melaleuca leucadendron*, usually the variety known as *Cajeputi viridiflora*, a shrub common to all of the East Indies Islands. The most valuable constituent of this oil appears to be the alcohol cajeputol ($C_{10}H_{18}$), a variety of cineol.

It is said to act as a carminative, stimulant, diaphoretic, parasiticide, and antiseptic. It is nonirritating and effective when dissolved in

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neutral fixed oils in dilution of 5 per cent. The redistilled oil which is official in the *Pharmacopoeia of the United States of America* should be specified for medicinal uses.

For a long time benzoin has been accepted as one of the best preservatives for fatty ointment bases, especially for lard, and it is generally conceded that its preservative strength increases with its hydroxybenzoic ester content. Parahydroxybenzoic acid esters have proved also to be of considerable value as preservatives for solutions containing alkaloids used in the treatment of eye conditions, more particularly in cases of surgery of the eye.

In their research work with animals Schubel and Manger demonstrated that the toxic effect of the disinfectant here used in effective dilution is so slight that it may be disregarded.

Sabalitschka in his studies of the germicidal value of the various esters of parahydroxybenzoic acid found that the propyl ester remained effective in a dilution of 0.05 per cent as here shown in his tables (Tables I and II).

TABLE I*

MIXED CULTURES OF STAPHYLOCOCCI, STREPTOCOCCI, AND B. COLI OBTAINED FROM HEAVY ORBITAPHLEGMON

| PROPYL P-HYDROXY-BENZOATE | CONCENTRATION | | | |
|---|---|---|---|---|
| | 0.03% | 0.04% | 0.05% | CONTROL |
| 24-hr. culture | ++ | + | – | ++++ |
| 48-hr. culture | ++ | + | – | ++++ |
| 72-hour culture | ++ | + | – | ++++ |

TABLE II*

PNEUMOCOCCUS WITH LEVITHAL AGAR

| PROPYL P-HYDROXY-BENZOATE | CONCENTRATION | |
|---|---|---|
| | 0.05% | CONTROL |
| 24-hr. culture | – | ++ |
| 48-hr. culture | – | ++ |

*The tabulation is taken from the report of Sabalitschka.[2]

Staphylococcus and mixed cultures in bouillon with 0.1 per cent parahydroxybenzoate were negative by reinoculation after twenty-four hours. Sabalitschka further states that the growth obtained from the above organisms on Levithal agar corresponded to results with other bacteria on agar-agar and the investigations with liquid nutrient media were in general somewhat better than on solid nutrients.

Since this propyl ester of parahydroxybenzoic acid is nonirritating, bacteriostatic in high dilutions, and directly soluble in oil, it has been used in the preparation of cajedrol in a dilution of 0.1 per cent.

As a medium to carry the cajeput oil and hydroxybenzoic ester we found the most desirable to be *Oleum archis* (American peanut oil, edible variety). This bland fatty oil has low viscosity, is nonirritating and an excellent solvent for volatile oil. It is light, less viscous, and less prone to rancidity than the olive oil or sweet almond oil generally

used in similar preparations. The oils and esters here described and used in making cajedrol are U.S.P. standard and are used in the following proportions:

| | |
|---|---|
| Parahydroxybenzoate (propyl) | 1 Gm. |
| *Oleum cajeputi* | 50 c.c. |
| *Oleum archis* in quantity sufficient to make | 1 liter |

These are readily obtainable in the United States and at comparatively low cost.

The effectiveness of cajedrol as an agent in relieving the distressing symptoms in many types of acute and chronic cystitis and other pathologic conditions of the bladder appears to be directly due to the therapeutic effect of the essential oil of cajeput plus the additional antiseptic or bacteriostatic action of the oil-soluble propyl ester of parahydroxybenzoic acid. The bland medium *Oleum archis* serves as a coating and protective film on the surface of the bladder wall.

During the past three years at the Brady Urological Institute we have used cajedrol in place of gomenol, which we formerly got from France. We have found cajedrol a soothing analgesic and a mild antiseptic. Cajedrol alleviates the distressing symptoms of various types of cystitis and other painful lesions, bladder tumor, prostatitis and vesiculitis, and the irritation that often follows instrumentation of the urethra and bladder. It is helpful in relieving bladder spasms which often are associated with these conditions, as well as allaying the symptoms of marked frequency, urgency, burning, strangury, and pain. We usually instill 10 to 15 c.c. into the bladder through a catheter at daily or biweekly intervals. Cajedrol is not a cure-all, but used in conjunction with established therapeutic procedures, it sometimes affords relief from distressing symptoms. In a few cases cajedrol has been injected up the ureter during the use of the Councill stone extractor and has facilitated withdrawal of this instrument when there has been some difficulty due to spasm of the ureter. We have noted no reactions or aggravation of symptoms in any patient from its use.

The following are examples of cases in which particular relief has been noted from the instillation of cajedrol into the bladder and urethra.

CASE 1.—M. G. (BUI 30325), a 38-year-old Greek housewife, had tuberculosis of the left kidney, ureter and bladder. Following left nephroureterectomy she complained of marked frequency, burning, urgency, and suprapubic discomfort and bladder spasms from ulcerative cystitis. The urine was cloudy and the bladder inflamed and ulcerated. An instillation of 1 ounce of cajedrol was made into the bladder daily for three weeks. Her symptoms were greatly alleviated, the urine became clear, and on cystoscopy the inflammation and ulceration of the bladder had decreased greatly.

CASE 2.—Mrs. F. G. A. (BUI 26856), a white woman, 38 years of age, had chronic urethritis and polyps of the bladder. She complained of great frequency, pain, and urgency of urination. She obtained relief from dilatation of the urethra, application of nitrate of silver to the urethra, fulguration of the polyps, and instillation of cajedrol, 1 ounce, on three occasions.

CASE 3.—H. D. (BUI 30245), a 64-year-old woman, had an ulcer of the bladder which had resulted from treatment elsewhere of carcinoma of the cervix with radium. She suffered from frequency, burning, pain, and strangury. Moderate relief followed the instillation of cajedrol every day for a week.

CASE 4.—F. E. T. (BUI 30403), a 59-year-old white man, had a history of chronic prostatitis, vesiculitis, and prostatic calculi. Culture of the urine yielded *Staphylococcus aureus*. He was improved by prostatic massage and diathermy, and the urine was rendered sterile by the use of sulfathiazole, but he still had moderate frequency, urgency, and some nocturia which were greatly alleviated by triweekly instillations of cajedrol into the bladder over a period of two weeks, after which he returned to work. Within two months his bladder capacity increased from 40 to 250 c.c.

CASE 5.—H. G. (BUI 27268), a 43-year-old woman, had chronic urethritis. She complained considerably of frequency, burning on urination, and urgency which did not respond to the usual forms of treatment, but upon having instillations of cajedrol on three occasions the symptoms were very markedly relieved.

CASE 6.—S. S., a woman 50 years of age, had chronic urethritis and urinary tract infection which was improved by the administration of sulfanilamide and local treatment for the urethritis, but moderate burning, urgency, and some frequency persisted. These symptoms were considerably alleviated by a few instillations of cajedrol.

CASE 7.—Z. M. (BUI 28570), a woman 41 years of age, had right renal tuberculosis and tuberculous cystitis. She suffered from marked burning, frequency, and nocturia. Following several injections of cajedrol she noted a decrease in the burning and absence of nocturia. Cystoscopy disclosed considerable improvement in the ulceration along the base of the bladder.

CASE 8.—W. S. (BUI 22442), a white man 50 years of age, returned after an absence of eight years because of terminal hematuria, marked frequency, burning, and urgency. Cystoscopy revealed a contracted bladder and marked cystitis. The urine was cloudy. He was given hydraulic dilatation of the bladder and instillations of cajedrol, 1 ounce, three times a week, for two weeks. Two months later there was marked alleviation of symptoms. He had only slight frequency, no urgency or burning, and the urine was clear. His bladder capacity had increased from 60 to 360 c.c.

CASE 9.—J. S. (BUI 28869), a woman 43 years of age, with urinary tract infection and chronic urethritis, suffered considerably from bladder spasms, nocturia, burning, and urgency. She was treated by antiseptics by mouth and local applications of nitrate of silver to the urethra, but only after being given cajedrol did she obtain considerable relief from her severe symptoms.

CASE 10.—N. A. (BUI 25688), a 71-year-old white man, following prostatectomy some years previously, returned with cloudy urine, considerable urgency, frequency, and burning. His bladder capacity was 50 c.c. He improved considerably following forced fluids and irrigations of the bladder with sulfathiazole, but the burning and urgency disappeared only after the instillation of cajedrol daily for ten days. The bladder capacity increased to 400 c.c.

CASE 11.—L. D. (BUI 1924), a middle-aged white man with a tumor of the bladder of long duration was given cajedrol two to three times a week for two months. The bladder capacity increased considerably; the frequency and urgency decreased.

We are indebted to Dr. Humphrey D. Wolfe, of Wilmington, Del., for a report on a series of cases in which he has employed intravesical injections of cajedrol.

CASE 12.—L. E. H., a 41-year-old man, complained of hematuria, marked frequency, and tenesmus. On cystoscopy the bladder was inflamed and congested, and there were numerous areas of submucosal hemorrhage. One bleeding area was fulgurated. Biopsy showed only necrotic material. He was given a daily instillation of 8 c.c. of cajedrol for seven days with relief of the urgency and frequency. Cystoscopy one month later showed marked improvement in the condition of the bladder and only a few discrete inflammatory lesions present. The bladder capacity increased from 45 to 260 c.c. within five weeks.

CASE 13.—L. G., a 44-year-old white man, complained of gross hematuria and frequency. On cystoscopy the bladder capacity was found to be markedly reduced. There were numerous hemorrhagic areas throughout the bladder, the mucosa of which had the appearance of raw beef. He was given daily instillations of cajedrol, 8 c.c., for ten days. His symptoms promptly disappeared. Examination of the bladder six weeks later showed a normal capacity and a normal mucosa, except for a few areas of congestion on the left lateral wall.

CASE 14.—L. R., a white man 53 years of age, had had periodic fulgurations of a bladder tumor for several months, but he usually was disturbed with painful bladder spasms and burning following these treatments. Intravesical injections of cajedrol, 10 c.c., resulted in marked benefit.

CASE 15.—H. M., a 65-year-old white man, who had been treated by fulguration and radium for a bladder tumor, had been bothered with marked frequency, nocturia, urgency, and burning. Daily injections of cajedrol, 10 c.c., resulted in marked relief of the frequency, nocturia, and strangury.

## SUMMARY

Products derived from plants of the Myrtaceae family have long been known to have considerable medicinal value. Of these cajeput oil has been shown to be of marked value. After much experimentation in the laboratory and clinic a combination of parahydroxybenzoate (propyl), *Oleum cajeputi* and *Oleum archis* was found to be a valuable compound for the relief of the distressing symptoms and many types of acute and chronic cystitis and other pathologic conditions in the bladder. This compound, to which the name cajedrol has been given, now has been used in many clinical cases. Brief abstracts of some of these cases have been presented. Cajedrol has proved to be a soothing analgesic and a mild antiseptic and a useful adjunct along with other well-established therapeutic procedures for the relief of distressing symptoms of general cystitis, interstitial cystitis, prostatitis, and also urethritis in the male and female. In some cases of marked ulceration of the bladder and tumor of the bladder, great improvement has been noted, as well as after instrumentation of the urethra and bladder. A marked increase in the capacity of the bladder has been noted in cases that received instillations of cajedrol. Other details showing the value of cajedrol in various vesical and urethral lesions have been cited.

Grateful acknowledgment is hereby made to Robert S. Fuqua, Chief Pharmacist, Johns Hopkins Hospital, for his valuable assistance and suggestions in the preparation of this paper. We wish also to express our appreciation to Dr. E. K. Marshall for his interest and advice on reviewing the manuscript.

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# MALIGNANT DEGENERATION IN A CASE OF MULTIPLE BENIGN EXOSTOSES

## With A Brief Review of the Literature

George E. Bennett, M.D., and George A. Berkheimer, M.D.,
Baltimore, Md.

*(From the Department of Orthopedic Surgery, Johns Hopkins Hospital)*

A CLEAR conception of the type of tumor with which we are dealing seems the best approach to this subject. The literature abounds with long and detailed classifications of cartilaginous and osteocartilaginous tumors, such as enchondroma, ecchondroma, osteochondroma, chondrodysplasia, etc. All these terms serve merely to differentiate bone tumors of cartilaginous nature according to the amount of calcified tissue they contain, their location, and their number. But they are all closely related, the enchondroma or chondroma being the most distant relative of the group in that it is almost completely cartilaginous in nature, occurs in the shaft of the bone, and frequently becomes malignant. On the other hand, all of the other mentioned types of tumors rarely undergo malignant change and occur most frequently in the metaphyseal region of the bone where it is believed an abnormality of development takes place. This consists in either a complete or partial arrest of periosteal extension across the metaphysis. Thus, there is lacking the usual limiting membrane of periosteum across the area and the underlying cartilage no longer has a restricted area of growth. Consequently an overgrowth of cartilage develops and tumor formation occurs. As these tumors become more mature, however, the cartilage usually becomes normal bone. Therefore, we feel justified in referring to them simply as exostoses. Certainly, their appearance in the x-rays below simulates that of bone of normal density. (Fig. 1.)

Actually, many years ago benign exostoses and chondromas were thought to be entirely different in composition, but as early as 1905 Lenormant[1] reported a number of analogies between the two conditions. Research progressed along these lines until in 1939 Kress[2] wrote that these two tumors are of the same origin but that exostoses are chronologically older and are fairly in line with normal bone development and that chondromas are composed of much younger tissue and, as is generally true of such tissue, undergo malignant change much more frequently.

### CASE REPORT

The history of this case of multiple exostoses is as follows: On May 15, 1940, while playing at school, the patient, a 10-year-old boy, was knocked down and the lateral side of the right thigh was bruised. The injury was not a severe one and was not disabling but served to attract the patient's attention to this region of

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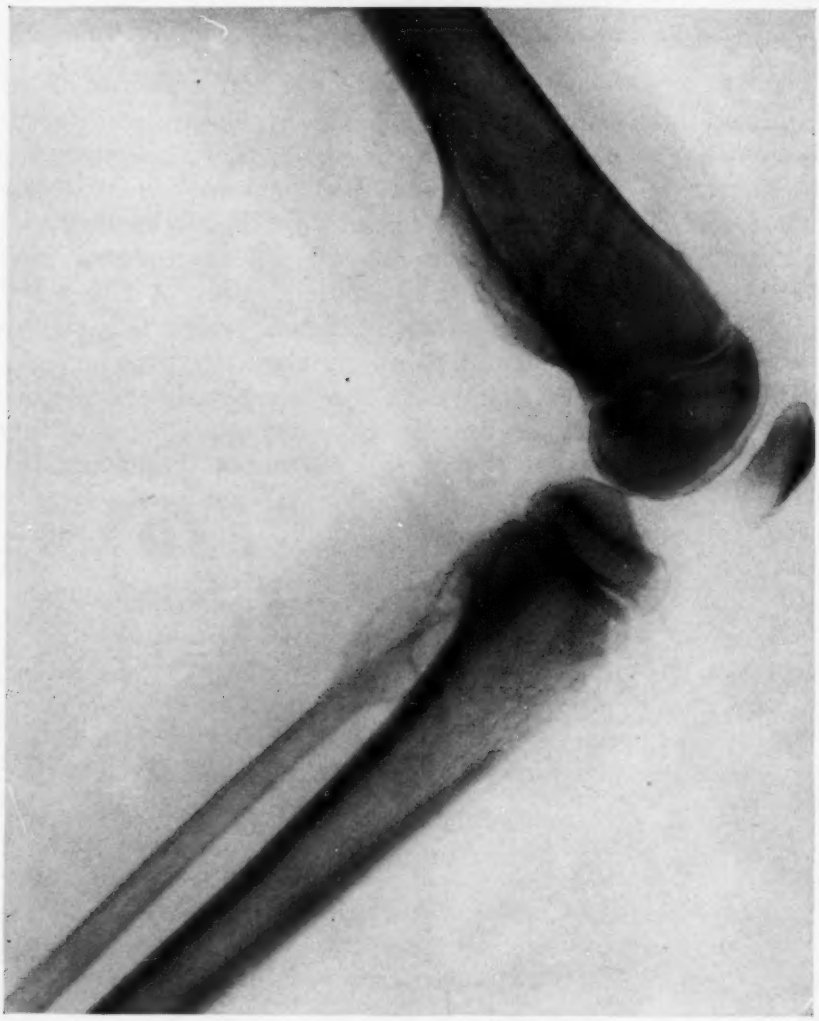
his leg where a swelling was now noted for the first time. It was tender and x-rays made at the time revealed the presence of a bone tumor. There was no history of weight loss or of other swellings or areas of tenderness.

The family history is best illustrated by the diagram shown in Fig. 2. From this it is seen that the disease affects both males and females alike and follows no laws of inheritance. Also, it is important to note that the patient is the only member of his family afflicted with malignant degeneration. The latest addition



*A.*

Fig. 1.—X-rays of the patient's left shoulder and knee, showing multiple benign exostoses.

to the family (represented by the solid circle in the extreme lower right portion of the diagram) was only 5 months of age at the time his x-rays were made, but close observation reveals several prominences in the metaphyseal regions that are very suggestive of the tumors found in his older relatives (Fig. 3). This, we believe, is one of the youngest known cases of multiple exostoses, the only other that approaches it being that of a 6-month-old child reported by Scott.[3]

Examination of this well-nourished, 10-year-old boy revealed a swelling of the right leg, just above the knee, on the lateral surface of the thigh, about two by two

Fig. 1*B*.—See opposite page for legend.

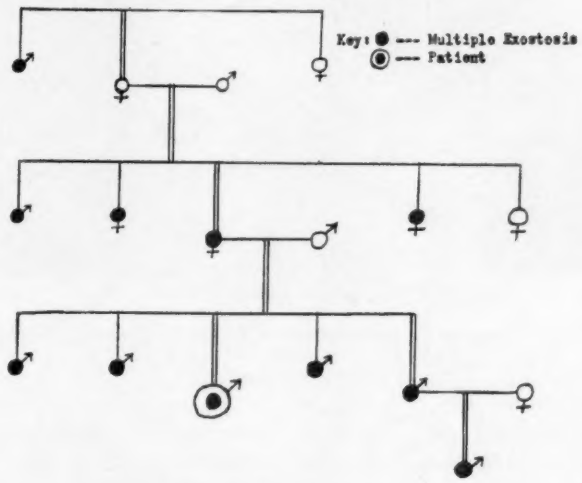



Diagram of the Family History

Fig. 2.—Diagram of the family history. From this it is seen that the disease affects both males and females alike and follows no laws of inheritance. Also, it is important to note that the patient is the only member of his family afflicted with malignant degeneration.

and one-half inches in size. It was hard and tender and a few superficial veins were seen in the overlying skin. X-rays revealed multiple exostoses scattered throughout the skeletal system. The one noted at the lower end of the right femur, however, was much more sclerotic than any of the others and, in addition, there was considerable periosteal reaction and some destruction of the cortex (Fig. 4). Accordingly, the tumor was biopsied and the section diagnosed as osteogenic sarcoma. Dr. A. Rich, of the Johns Hopkins Medical School, pointed out the intense

*A.*

Fig. 3.—X-rays of the patient's five-month-old nephew, showing the lower ends of the right forearm and left upper leg.

cellular growth activity with frequent mitotic figures in the section shown in Fig. 5. A great variety of cells is present. There are large cells with large, hyperchromatic nuclei; smaller cells with pale, indefinite cytoplasm and containing oval or irregular-shaped nuclei; spindle-shaped cells and several other types of less frequent occurrence. Among these are scattered osteoid spicules forming a sort of "lattice work." (Fig. 5.) X-rays of the chest, however, were negative and there was no glandular enlargement indicative of metastases. The child's parents,

however, refused permission for additional operative procedures and preferred resorting to deep x-ray therapy, although authorities agree that this is effective to only a slight degree in this type of tumor. This treatment was administered three times a week during the month of August, 1940, but since then it has been given only twice a week. By using alternating sides of the leg for approach, x-ray burns have been avoided and treatment has been uninterrupted. Follow-up x-rays have revealed that the tumor is slightly increased in size and that it is becoming increasingly sclerotic (Fig. 6). The chest continues clear. The patient looks well and there are no evidences of metastases.

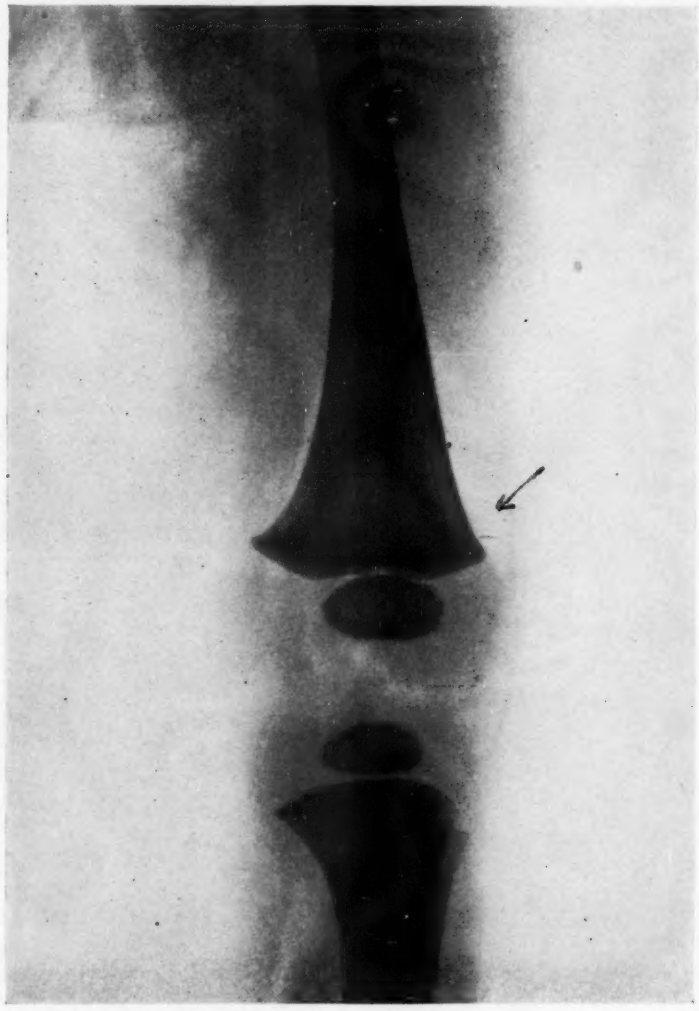


Fig. 3*B*.—See opposite page for legend.

It is impossible to make any conclusive statements regarding these malignancies on the basis of the limited number of cases at our disposal, but certain generalizations do seem to be taking form. First of all, the frequency of malignant degeneration in cases of multiple, benign exostoses seems to have been greatly exaggerated and apparently many conflicting statements have been made regarding this point. Most references and series, however, relate to single exostoses in which cases

Geschickter and Copeland[12] state that malignant degeneration occurs so frequently as to be present in 7 per cent of all cases. This figure seems abnormally high and may well be explained by the fact that the vast majority of ordinary exostoses are asymptomatic and are never seen by physicians. Usually a doctor is consulted only when they become painful or produce paralysis through impingement on a nerve or suddenly

A.

Fig. 4.—X-rays of the lower end of the right femur.

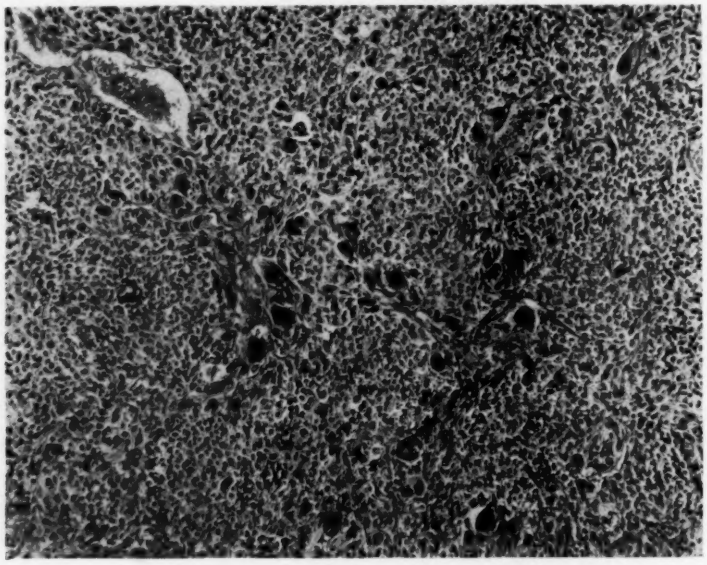
increase in size, as is the case in malignant degeneration. No substantial series of malignant degeneration in cases of multiple exostoses has ever been compiled; in fact, isolated case reports occurring at very infrequent intervals are all that the literature has to offer. American authors present three clear-cut cases. One is that reported by Jeck[5] in a patient in whom one of a number of enchondromas underwent

malignant change and then invaded the bladder. Fennel,[6] in 1938, described another occurring at the site of an exostosis of the femur and Codman had a patient whose leg, and later, whose arm, he had to amputate because of malignant degeneration of an exostosis of the femur and of the humerus. Ehrenfried,[7] in 1915 reviewed multiple exostoses in general and was able to report only twelve cases; of these he does not give any case history or evidence of their malignancy, yet states that

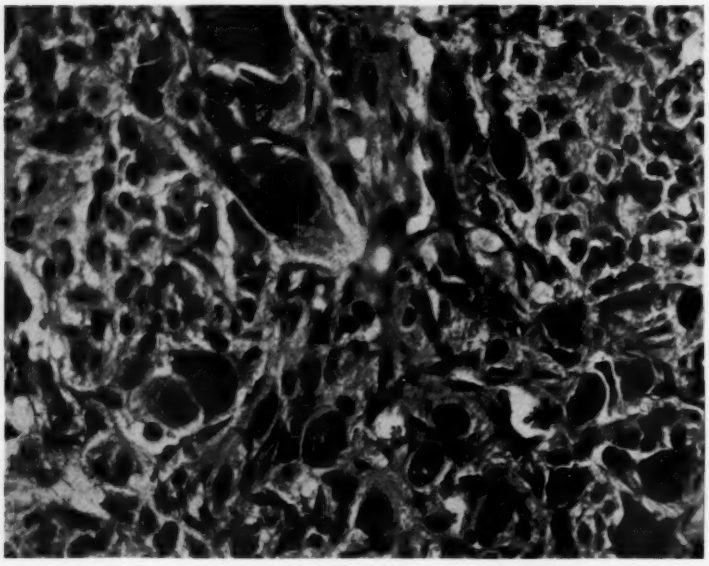
Fig. 4*B*.—See opposite page for legend.

malignant degeneration occurred in 5 per cent of all cases. He quotes two French authors, Lenormant and Lecene, who in 1905 collected twenty-four cases, most of which were fatal; but, in view of the infrequency of this change, it is hardly probable that such degeneration was the cause of these fatalities. Also, isolated and infrequent cases have been reported in the foreign literature: Belot and Simchowitz,[8] in 1936,

reported a well-established case of malignancy evolving from one of many benign exostoses, this occurring in the humerus; and Ciechanowski,[9] writing in the same year, reported a case of spindle-cell sarcoma in a patient with multiple exostoses. This terminated fatally, there being metastases in the liver. Didier,[10] in 1935, reported a case of chondrosarcoma of the sternum following the resection of a benign exostosis from the same site. And finally, Gardner,[11] in 1937, reported two cases that underwent malignant change. Both were treated with deep x-ray therapy; the one died of heart failure and the other was living at the



*A.*



*B.*

Fig. 5.—Microscopic views of the section biopsied from the lower end of the right femur. *A*, Low power (×100); *B*, high power (×400).

time the paper was published in 1939. In short, a review of the literature reveals that malignancy does occur in cases of multiple benign exostoses, but that it is a rare and infrequently reported complication. It is interesting to note that the later writers all consider malignant degeneration a very rare development in these cases, in contradistinction to the earlier authors who really had fewer and less convincing case reports but who spoke rather rashly of the relatively great frequency with which such tumors underwent malignant change.

The pathologic picture presented by those exostoses which undergo malignant degeneration is generally reported as that of an osteogenic sarcoma, although cases of chondrosarcoma and spindle-cell sarcoma have been described. Geschickter[13] feels, however, that these osteogenic sarcomas usually contain more cartilaginous tissue than does this case in which the "lattice work" seemed composed entirely of osteoid spicules. But in marked contrast to the usual short duration of life with early metastases, which is the usual story accompanying these tumors, most cases of malignant change occurring in a pre-existing exostosis have relatively long life spans. This may be explained by Copeland's[14] statement that osteogenic sarcoma is a term loosely applied to a group of bone tumors that differ markedly in their histology and degree of malignancy. At any rate, Fennel, whose case we have previously mentioned, reported an Hawaiian named Hong Mun, but who was better known as "Knobby Willy—the Exostotic Kid," in whom malignant degeneration occurred at the site of an exostosis of the femur. A sharp and thorough dissection was carried out, the patient refusing amputation. Pathologic sections confirmed the diagnosis of osteogenic sarcoma. Follow-up treatment consisted only of the implantation, for twenty-four hours, of some radium seeds. Thirteen and one-half years later the patient was perfectly well and actively employed at house painting. Codman's case, too, was free from recurrence ten years after the amputation of a leg and an arm. Gardner's cases, which were treated with deep x-ray for several years, died of causes other than metastases. So it does seem highly probable that Codman's suggestion in 1925 that osteogenic sarcoma arising in an exostosis has a better prognosis than the usual kind was a clear prediction of future findings.

There has been some speculation, too, regarding the factor concerned in the malignant degeneration of these exostoses. In this case there was a history of trauma, but this injury served only to lead to discovery of the tumor and x-rays taken several weeks later showed malignant change of a degree incompatible with the length of time intervening between the date of injury and the x-ray. Kress feels that an exogenous factor, such as trauma, is concerned but that also an hereditary factor is present. In contradiction of both of these theories is the case history of our patient as well as those of two even more completely investigated cases reported by Gardner. In all three instances the patients were

the only members of their respective families so afflicted; but of the seven or eight complete histories found in the literature, the traumatic factor is present in approximately 70 per cent. At the present time it seems that the fundamental elements concerned in the malignant degeneration of a benign exostosis remain rather obscure, yet trauma does seem of some importance.

*A.*

Fig. 6.—X-rays of the lower end of the right femur in July, 1940 (*A*), and November, 1940 (*B*).

Finally, there is the question of treatment. We believe that most surgeons would feel as did Rich, who upon looking at a microscopic section of this tumor said: "If that tumor were in my leg, I should want it amputated immediately." Certainly, the extremely malignant appearance of these sections would provoke such a reaction, yet because of the

natural objections to amputation as well as the inability to guarantee against metastases or recurrence, there are a number of cases similar to this in which amputation was refused and deep x-ray was used. Geschickter, however, states that osteogenic sarcomas respond in only "slight degree" to such therapy. Similarly, the observers of the New York Memorial Hospital feel that deep x-ray has no effect at all on these malignancies. Yet our patient at the present time has no evidence

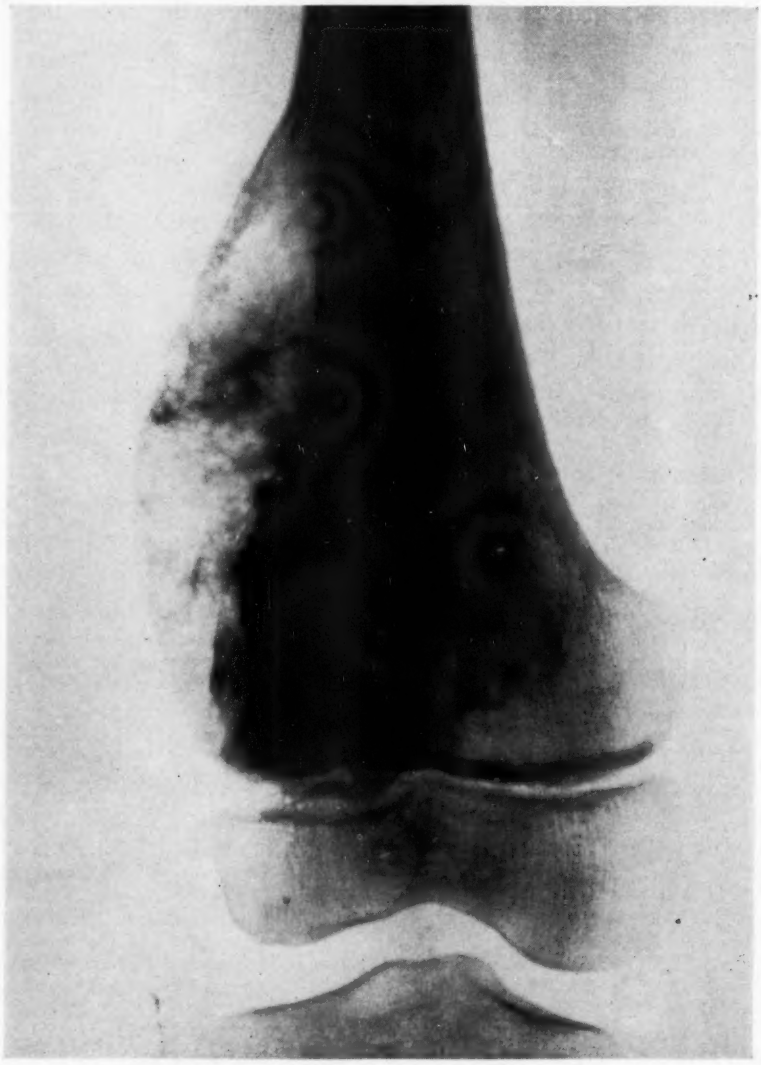


Fig. 6*B*.—See opposite page for legend.

of metastases and his tumor has increased only slightly in size. Gardner reports a case in which deep x-ray was used for two and one-half years, at which time the patient died of heart failure. He does state, however, that the tumor mass became larger during the course of treatment and that the patient became very emaciated. There are positive records of

long-term cures following amputation, Codman reporting one of ten years, Boyer another of eighteen years, and Fennel one of thirteen and one-half years. In view of these facts, it would seem that amputation is the treatment of choice, but in those cases which are inoperable or in patients who refuse amputation a trial with deep x-ray therapy certainly seems indicated.

## SUMMARY

1. A case of multiple, familial, benign exostoses in which malignant degeneration evolved from one of the exostoses is described.

2. Malignant degeneration of multiple exostoses is a rare complication.

3. The fundamental cause of malignant degeneration in multiple exostoses is obscure, although trauma seems a factor.

4. The type of malignancy most frequently complicating cases of multiple exostoses is an osteogenic sarcoma.

5. The osteogenic sarcoma complicating multiple exostoses is a less malignant form than that usually encountered.

6. The treatment of choice is amputation, but the use of deep x-ray therapy is indicated in those patients refusing such an heroic measure and in those cases which are inoperable.

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# THE PARATHYROID GLANDS
## MALIGNANT TUMOR WITH OSTEITIS FIBROSA CYSTICA

R. J. Gentile,* M.D., Seattle, Wash.
H. L. Skinner,† M.D., Baltimore, Md., and L. L. Ashburn,‡ M.D.,
Washington, D. C.
*(From the Surgical Service, U. S. Marine Hospital, Baltimore, Md.)*

THE parathyroid glands, usually four in number, grow as paired structures from thickenings of the endoderm of the third and fourth branchial pouches. Their development is entirely independent of the thyroid gland. The superior pair of glands arise from the fourth pouches and are sometimes called "glandulae parathyroideae IV." The inferior pair are derived from the third pouches and are sometimes called "glandulae parathyroideae III." This transposition is brought about by the caudal migration of the branchial derivatives during which the thyroid gland and the "glandulae parathyrideae IV" have been outdistanced.

The extremely close relationship of the parathyroid glands to the thyroid and thymus is accountable for the not infrequent presence of one or more parathyroid bodies within the tissues of these two glands. Although thymus tissue has been found within the parathyroid glands, no thyroid tissue has ever been discovered therein.

A human being usually possesses four parathyroid glands. However, many variations in number have been found. In some cases experienced dissectors, such as Valkanyi,[1] have been able to find only one gland. MacCallum[2] has been able to find five pairs of these glands in one person. Symmetry may not be constant. Failure to find at least four glands may be attributed to one or more of the following causes: (1) congenital absence of one or more glands, (2) inclusion within the thyroid or thymus glands, (3) abnormal position and asymmetry of the glands, and (4) unskilled or impatient dissectors.

Each gland may show marked variations in size, shape, weight, and sometimes color. Each may vary from 3 to 15 mm. in length, from 2 to 4 mm. in diameter, and from 0.5 to 2 mm. in thickness. The size of any one body is thought to be dependent, in part, on the total number present, the ratio being an inverse one. Because of the soft, flabby, and yet inelastic consistency of the gland, the shape is easily altered by the pressure of structures.

Pappenheimer and Wilens[3] found that the average weight of the upper glands ranges from 0.027 to 0.032 Gm. each. The lower glands

*Passed Assistant Surgeon, U. S. Marine Hospital, Seattle, Wash.
†Surgeon, U. S. Marine Hospital, Baltimore, Md.
‡Passed Assistant Surgeon, National Institute of Health, Washington, D. C.
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were found to be approximately 20 per cent heavier. In females, during active sexual life, the parathyroids have been found to be even an additional 20 per cent heavier.

In infancy and childhood the glands are a light yellowish red, and with increasing age there is a gradual darkening to a yellowish brown or reddish brown color.

The superior pair are more constant in position and usually are found on the posteromedial surface of the thyroid lobes at about the level of the junction of the upper and middle thirds of this structure. The inferior pair are commonly found on the posterior surface of the inferior pole of the thyroid. However, their positions may vary from the angle of the jaw to the anterior mediastinum, and from in front of the thyroid to a position posterior to the esophagus.[4-7]

The blood supply of both upper and lower pairs is received from branches of the inferior thyroid artery. The superior pair may occasionally be supplied by a branch from an anastomosing trunk of the superior and inferior thyroid arteries. The arteries are of the terminal or "end" type.[8]

The nerve supply is furnished by a few, nonmedullated nerves, vasomotor in function, which arise in the middle and inferior ganglions of the cervical sympathetic trunk.[9]

Thus far, there has been no detailed study of the lymphatics.

Prior to 1935 confusion existed as to the types of cells composing the parathyroid glands. In that year, Castleman and Mallory[10] recognized four major cell types with transitional forms. Morgan[11] in 1936 studied the cytology of over 300 normal glands. He also recognized the same four cell types: i.e., the pale principal cell, the dark principal cell, the dark oxyphilic cell, and pale oxyphilic cell. He stated that the pale principal cell is the primary one from which all other types arise in the order just described.

The essentially basophilic pale principal cells comprise the bulk of the gland, and although present throughout life, they decrease relatively in number with advancing age. They are round to polygonal in shape, with a diameter of 7 to 15 microns, with a nucleus measuring 5 to 6 microns. The cytoplasm consists of an irregular network of particles of various sizes. When these particles are stained by the pyronine methyl-green method, they appear light red. Vesiculation is present, and as this increases, the cytoplasmic network is pushed to the periphery. This increases the prominence of the limiting membrane. When vesiculation is extreme, the nucleus appears to be lying free in an empty cell.

The dark principal cells are present in infancy and increase in number relatively with advancing years. They are smaller than the pale variety, the diameter measuring from 6 to 12 microns. The cytoplasmic network is irregularly fragmented and vesiculation is present. The nucleus is small. It measures 3.5 to 5 microns in diameter, is irregular

in shape, contains closely packed chromatin granules, and takes a deeper stain than the nucleus of the pale type.

The dark oxyphil cells are relatively few in number. They measure from 6 to 14 microns in diameter, are polygonal in shape, with oxyphilic cytoplasm almost or entirely filled with granules of a fairly uniform size. The nucleus is similar in appearance to that of the dark principal cell though slightly larger (4 to 5 microns).

The pale oxyphil cells are more numerous than the dark oxyphil cells. They are irregularly polygonal and are very large (9 to 15 microns). The cytoplasm stains reddish pink with hematoxylin and eosin and contains many granular masses. The nucleus is 4 to 6 microns in diameter, is paler than that of the dark oxyphil cell, has a homogenous appearance, and is usually toward one side of the cell.

In each cellular type, fat and glycogen have been found, but more predominantly so in the principal cells.

The cells frequently appear in rows or columns which are folded on themselves. Acini are found in glands of all ages. The cells lining the alveoli tend to be low columnar or cuboidal and generally are the principal cells. The number of acini and the position within the gland are extremely variable. They usually contain a clear colloid material which stains evenly with eosin. The oxyphil cells tend to appear in groups near the poles and periphery of the gland.

The physiologic significance of each cell type is not known. Since the principal cells are almost the only variety found in infants and young children during the period in which bone formation is most active, Morgan[11] concluded that these cells mostly were responsible for the secretory activity concerned in the role of the parathyroid glands in calcium metabolism.

## CONSIDERATION OF MALIGNANCIES

Recognition is given to Sandstrom[12] for having first described the parathyroid glands in 1880. From the first description until 1926 the relationships of these glands remained more or less a mystery. In 1926 Mandl[13] proved their importance to the skeletal system by producing alleviation of calcium metabolic abnormalities in a case of osteitis fibrosa cystica by removal of a parathyroid tumor. This finding created new interest in the physiology and pathology of the parathyroids, resulting in a vast amount of literature on these structures.

Between 1880 and 1926, many tumors of the parathyroid glands were reported. In the last decade the number has run into the thousands. An overwhelming majority of these tumors were benign. Malignancies have been reported rarely, only twenty-one being found in the medical literature.

In 1909, Kocher[14, 15] reported eight cases in which the tumor was usually present for years. Three were females; five were males. The

ages ranged from 46 to 61 years. The tumors ranged in size from small nodular "rests" to one 12 by 9 by 9 cm. Two tumors were in the midline, four were on the left side, and the position of the other two was not stated. No bony changes were noted. These tumors were usually nodular, fixed, either hard or elastic. Histologically, they were characterized by large transparent cells with sharp red boundaries and the absence of granular eosin red protoplasm but containing varying amounts of glycogen. Presence of this glycogen prompted the name "glycogenous goiters of Kocher." Sarcomatous-like tissue was also present and in some instances even giant cells were found.

In 1909, De Quervain[16] reported a case in which there was invasion of the jugular vein and the sternocleidomastoid muscle, and five months later pulmonary metastasis as well as local recurrence developed. The tumor showed the typical arrangement of the parathyroid gland. The patient was a male, aged 68 years, in whom no bony changes occurred. The tumor was located on the right side of the neck and was 6.5 cm. in diameter.

In 1914, Roffo and Landivar[17] reported a case of a mediastinal tumor adherent to the surrounding structures and which pulsated with the pulsation of the aorta, simulating an aneurysm of the arch of the aorta. However, its volume did not increase with the pulsations. The removed tumor, 10 cm. in diameter, was lobulated and possessed a fibrous capsule which sent many trabeculae into the mass, some of which contained calcium deposits. The sectioned tumor was grayish white, contained many cavities of various size which contained colloidlike material. Other portions showed hemorrhagic areas. Histologically, the tumor tissue was composed of follicles with columns of cylindrical cells containing nuclei in mitosis. Frequently, the proliferated epithelium possessed large vesicular nuclei. In the metastasis which later occurred in the thyroid gland, lungs, and liver, the predominating cells were elongated and polyhedral cells with well-defined limits. The patient was a male, aged 60 years, in whom there were no bony changes. The tumor was on the left side at the lower pole of the thyroid.

In 1923, Fasiani[18] reported a case of a tumor 10 cm. in diameter, elastic and movable, nodular, and containing many cavities and solid nodules. Tumor tissue corresponded to that of the parathyroid gland. Mitosis and invasion of the thyroid gland were marked. The patient was a female, aged 65 years, with no evidence of bony changes. The tumor was situated in the left side of her neck.

In 1925, Ferrero and Sacerdate[19] reported a case of a tumor developing in the femur which was fractured by the examining physician. This tumor possessed the structure of the parathyroid gland. One month after the fracture of the femur, an apparently benign metastasis appeared in the right temporal bone. A small tumor, which had been

present in the right side of the neck for fourteen years, was found. The patient was a female (age not stated) with no other bony changes than that described.

In 1927, Alessandri[20] reported a case of combined thyroid and parathyroid tumor of the right humerus with metastasis to the shoulder (previous history of two injuries to the shoulder). Although no tumor was found in the neck, the tissue simulated parathyroid gland structure. The cells were neatly defined, largely polyhedral, with light-staining protoplasm, situated in a stroma of thin connective tissue with numerous broad and varicosed capillaries. The central, well-eosin-stained nuclei contained plenty of chromatin. The patient was a male, aged 51 years, with no other bony changes.

In 1929, the tumor observed in a 34-year-old female at the Mayo Clinic by Wellbrock[21] and also Wilder[22] measured 5 by 3.5 by 3 cm. and was situated at the lower pole of the right thyroid gland. It was nodular, fluctuating, and semielastic in consistency and clothed in a fibrous capsule. On section, it consisted of four distinct encapsulated nodules composed of yellowish brown, fairly firm, and reddish blue spongy tissue, containing several cavities varying in size and filled with amber-colored fluid. Microscopically, the neoplastic portion of the nodules was composed of large, clear cells with poorly staining cytoplasm, polygonal in shape and containing variable sized nuclei with deeply staining, coarsely granular chromatin material. There were also bandlike masses of more deeply staining cells in which the cellular limits could not be seen very clearly. Many mitotic figures were present.

This case, in addition, showed local and diffuse decalcification of the bones with hyperparathyroidism.

In 1929, also, Guy[23] reported a case in a female, aged 29 years, in whom the tumor was situated behind and below the left lobe of the thyroid and measured 8 by 6 by 4 cm. The cut surface revealed a cortical yellowish portion and a grayish medullary gelatinous portion. Histologically, the tumor consisted of the clear type of cells arranged in columns. No oxyphilic cells were seen. Biopsy was done eleven months later on three recurring nodules on the neck. In this latter tissue, there was a marked variation in the size, shape, and chromatin content of the cells. Mitotic figures were abundant. The palisade arrangement was lost, and the cells grew in great confusion. They were seen infiltrating the surrounding soft tissues and growing into the endothelium-lined spaces in which they were found in masses.

In 1931, Toland[24] reported a case in a female, aged 60 years, in whom the tumor was found at the upper pole of the right lobe of the thyroid and densely adherent to the surrounding muscles. No histologic report accompanied the case description, but Hall,[27] two years later, studied the slides and found it to be adenocarcinoma of the parathyroid. Irregular, atypical cells of various sizes and shapes possessing large hyper-

chromatic nuclei were seen. The cells were arranged in a haphazard fashion. Mitotic figures were present but in some sections hard to distinguish.

In 1932, Price and Mowat[25] reported a case in a 49-year-old male in whom the tumor was found behind the angle of the left jaw. The mass was the size and shape of a hen's egg, and because it appeared at the angle of the jaw, they believed it to have developed from a parathyroid rest. Because of the infiltrative invasion of the surrounding tissues, including the internal carotid artery, only portions of the neoplasm could be removed, and radium therapy was instituted. Histologic examination of one part of the tissue revealed normal appearing parathyroid cells in palisade formation with scattered areas of alveolar formation. Sections from other parts of the mass showed a somewhat similar arrangement, but the cells were large and polyhedral in shape with large nucleoli and marked vacuolization of the cytoplasm. Many areas of necrosis were present.

In 1933 Sainton and Millot[26] reported a case (the age and the sex of the patient were not given) of malignant adenoma in a case of hyperparathyroidism with osteitis fibrosa cystica. The tumor was situated in the left lower parathyroid gland, was about the size of a "green walnut," was covered by a dense fibrous capsule, and invaded the surrounding tissue. Microscopically, the variable sized, dedifferentiated tumor cells were round or polygonal. The cytoplasm was abundant, with finely granular character, and stained eosinophilic. Borders of the cells were indistinct. The pyknotic nuclei were centrally placed, were very basophilic, with chromatin divided in lumps. Mitosis and cellular necrosis were present.

In 1934 the case of Hall and Chaffin[27] was reported. The patient was a male, 46 years of age, who exhibited no bony changes. The tumor, 11 by 8 by 5 cm., was located in close proximity to the left lobe of the thyroid, and invaded the band muscles of the neck. Sections from various parts of the tumor showed anastomosing cords and columns of atypical epithelial cells which had invaded the surrounding muscle tissue in places. In other parts the tumor was limited by a fibrous capsule. Scattered fibrous tissue bands crossed the tumor. In a number of places large cell masses appeared in which the alveolar arrangement was not very evident. The nuclei of the epithelial cells were round or oval, vesicular, and moderately deep staining. They contained one large and often one or two small nucleoli. The nuclei were variable in size; some of them appeared quite large. Occasional mitosis was seen. The cells were polygonal in shape with abundant, finely granular, moderately eosinophilic cytoplasm. Some groups of cells had clear cytoplasm. Other groups of cells, which had a tendency to be elongated or fusiform, had hyperchromatic nuclei and more deeply staining cytoplasm. These cells had a loose, nondescript arrangement and appeared to be distinctly atypical. In several places, masses of tumor cells were seen in the small

and medium-sized veins of the stroma. Other cell groups about the border of the tumor appeared to be in the lymphatic vessels.

In 1936 Snell[28] reported a case seen at the Mayo Clinic in a male 47 years of age. The tumor was found at the lower pole of the right lobe of the thyroid gland, behind the trachea, and slightly under the sternum. It measured 6 by 6 by 5 cm., was smooth and covered with a plexus of veins. No histologic description was given. The diagnosis rendered by the pathologist was carcinoma of the parathyroid gland, Grade I.

This case also exhibited hyperparathyroidism with miliary osteoporosis.

In 1938 Armstrong[29] reported a case in a 71-year-old female, the tumor being situated on the right side of the neck. It measured 11 by 11 by 4 cm., was stony hard, reddish brown, and covered with a dense fibrous capsule. It was adherent to the internal jugular vein and the sternocleidomastoid muscle.

The cells were arranged in loosely packed masses and long columns. They were round and oval, large in size, with abundant acidophilic cytoplasm containing clear vacuoles. The nuclei were well stained. Mitosis was not reported. The diagnosis was carcinoma.

## REPORT OF CASE

J. A. S., white male, aged 38 years, a machinist, was admitted to the U. S. Marine Hospital, on Oct. 17, 1936, with the chief complaint of "broken legs, arm and shoulder." While attempting to climb up a flight of stairs, his legs became weaker than usual; he could no longer stand up and fell. He did not fall very far, only about the height of four ordinary steps. However, he was unable to get up unassisted.

For one and one-half years previous to admission the patient had been annoyed by what was thought by his family to be arthritis, yet the joints of the body were not necessarily affected. At times during this period his ankles and knees had become terribly painful and extremely swollen. In addition, pain was experienced in the shoulders, particularly the right. Occasionally he experienced "muscular pains" most marked in the legs, which he described as "sharp, shooting" pains. Polyuria had been present for years.

Since onset of the pains, he had become slowly, progressively weaker, was unable to do the work he had previously done, and had lost eighteen pounds of weight. He had not noticed any decrease in height. On the day before admission, he experienced a sore throat. For the first time he noticed a small lump in his neck just above the sternal end of the left clavicle.

Physical examination revealed a poorly developed, poorly nourished 38-year-old, pale, white male, who appeared much younger than his age. In the neck just above the sternal end of the left clavicle was a mass which was hard, firm, nodular, and unattached to the skin. Its size approximated that of an English walnut and was in the region of the left lobe of the thyroid gland. The teeth were very carious. The heart exhibited a soft, blowing diastolic murmur, best heard at the apex. The point of maximal impulse was in the sixth left interspace 2 cm. beyond the midclavicular line. The pulmonic second sound was greater than the aortic second sound. Blood pressure was 170/100. The blood vessels were normal. Mucous membranes were pale and possessed a yellowish color.

Urinalysis showed a specific gravity of 1.009 and a trace of albumin. Kahn test was negative. Red cell count, 4,200,000; white cell count, 18,000; hemoglobin 65 per cent. Differential smear revealed neutrophiles, 80 per cent; small mono-

nuclears, 19 per cent; and transitionals, 1 per cent. Blood sugar was 80 mg. per 100 c.c. of blood. Blood calcium was 14.7 and blood phosphorus 3.4 mg. per 100 c.c. of blood. Phenolsulphonphthalein test totaled 20 per cent after two hours. Mosenthal concentration test showed greatest specific gravity to be 1.007. Test for Bence-Jones bodies was negative. Electrocardiogram revealed only sinus tachycardia. Roentgenologic findings were as follows: "The right humerus shows a fracture at the surgical neck with the fragments in good position. The left femur shows a fracture through the middle third with slight posterior displacement of the lower fragment. The right femur shows a fracture of the upper third with the fragments in good position. The bones in this case show an outstanding condition. There is absorption of the calcium from the center of the bones to the cortex. The bones, in areas, show only a shell-like structure remaining, being only slightly more dense than the soft tissues." (Figs. 1 and 2.)

The other bones were x-rayed and "the left humerus, scapulae, clavicles, and, to a lesser extent, the ribs show similar changes to those previously reported in the femurs, pelvis, and right humerus. None of these changes are seen in the skull or the left forearm."

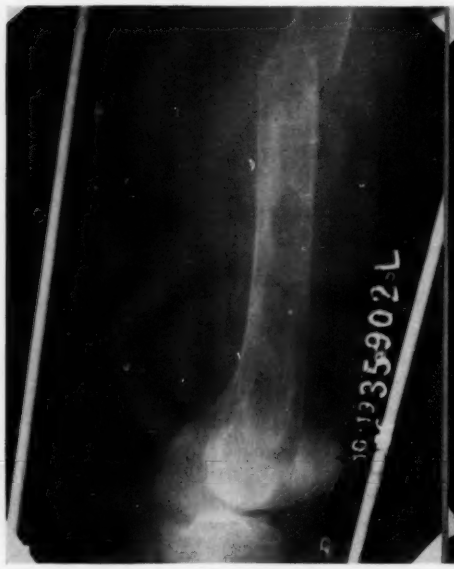

Fig. 1.

Fig. 2.

Fig. 1.—X-ray of left femur on admission showing marked decalcification and a fracture through the middle third.

Fig. 2.—Right humerus with marked demineralization and fracture of the surgical neck. Arrow indicates ring of calcium deposit within tumor.

The fractured members were immobilized by plaster casts. Repeated blood chemistry showed a persistent high calcium and low phosphorus. Therefore, on Nov. 16, 1936, an exploratory operation of the neck was performed under local (1 per cent novocain) anesthesia. A hard, nodular tumor (Fig. 3) was found in the region of the left lobe of the thyroid gland, densely adherent to this gland, but not actually a part of it. The mass measured 5 by 3 by 2 cm., was reddish brown in color, and possessed a ring of calcium at one end. This calcified ring was previously seen in the x-ray film taken primarily to show the condition of the right humerus and ribs (Fig. 2). X-rays of the removed mass showed the calcification within the mass (Fig. 4).

The specimen was sent to the National Institute of Health, Washington, D. C., for histopathologic study. The report is as follows: "Left parathyroid has a thick, densely fibrous capsule and trabeculae [Fig. 5], which show patches of

lymphocyte and plasma cell infiltration, an occasional small area of calcification and few foreign body granulomata, in which large angular spaces occur, presumably cholesterol clefts. The parenchyma [Fig. 6] is formed of large and small sheets, nests, and columns of cells enclosed by or embedded in the dense fibrous tissue. Tumor cells are polygonal and medium to large in size. They have much reticulogranular oxyphilic to amphophilic cytoplasm with distinct cell borders. Nuclei are medium to large in size, vesicular, usually centrally located, commonly have one or more large nucleoli, and are moderately and occasionally marked hyperchromatic [Fig. 7]. Few cells are binucleate and rarely a multinuclear cell is seen. Few mitoses are present. One medium sized venous channel shows invasion of its wall by an adjacent tumor nodule [Fig. 8]. In many areas small, poorly circumscribed cell nests occur, and few of these show infiltration of the surrounding fibrous tissue. The larger cell sheets occasionally show focal coagulation or karyorrhectic necrosis.

Fig. 3.—Reddish brown, hard, nodular tumor removed at operation.

Fig. 4.—X-rays of tumor mass removed at operation, showing within the growth the calcium deposit noted in Fig. 2.

"Little striated muscle and less thyroid tissue is adherent to capsule.

"Diagnosis: Adenoma of parathyroid (malignant?)."

Immediately after the left parathyroid gland was removed, the blood calcium fell rapidly with an irregular level of blood phosphorus (Fig. 9). Large doses of calcium salts (gr. 225 daily), viosterol, and a high calcium diet were given. Although the blood calcium fell below the established critical level, the patient showed no signs of tetany. As the blood calcium reached the normal level, the calcium therapy was less intensive.

Fig. 5.—Low-power view of tumor showing peripheral layer of fibrous tissue continuous with the lobulating trabeculae (×16).

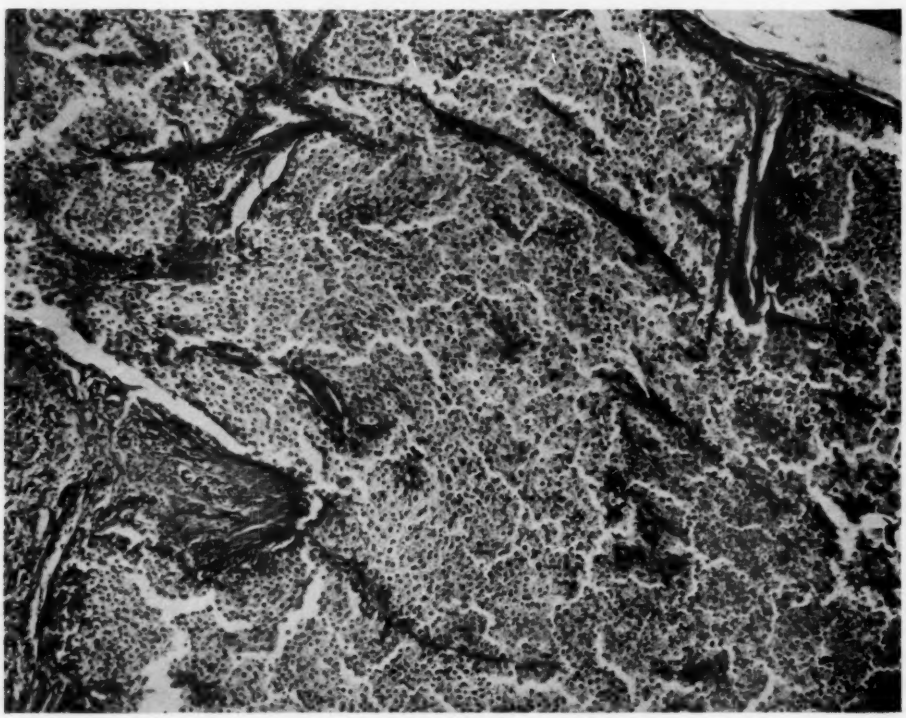

Fig. 6.—Photomicrograph showing general tumor structure (×128).

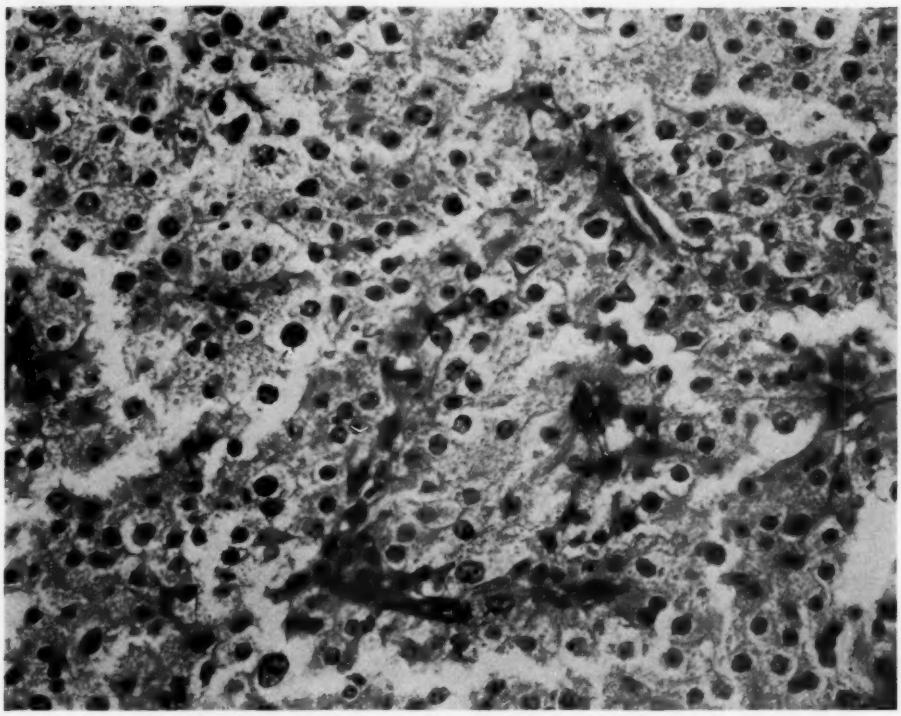

Fig. 7.—High-power view, showing variation in nuclear size, nuclear hyperchromasoa, granular cytoplasm, and distinct cytoplasmic borders (×500).

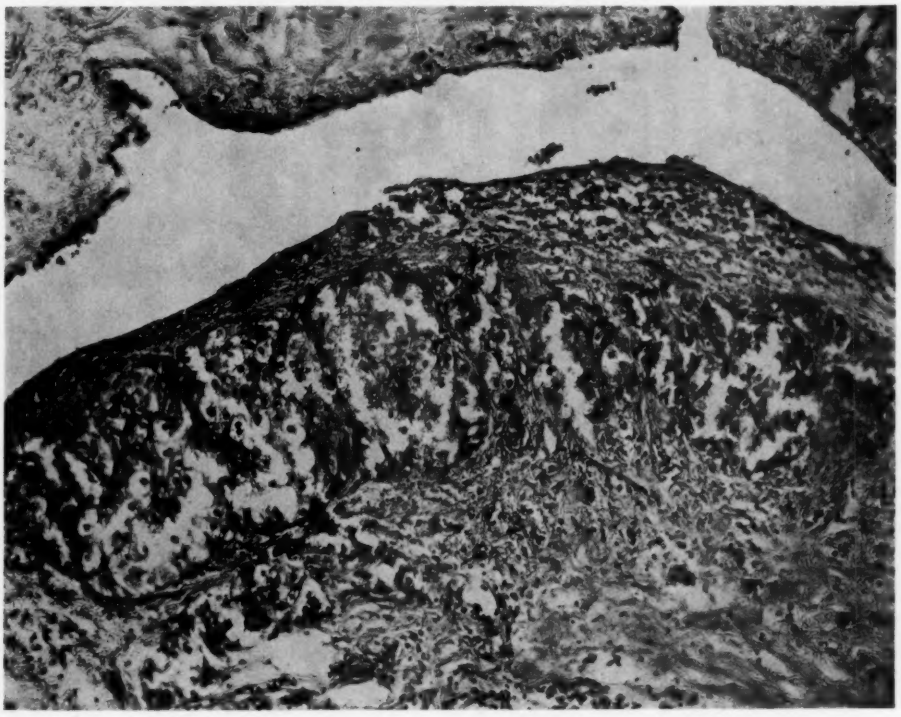

Fig. 8.—Tumor mass invading wall of wide vascular channel (×210).

The patient's condition generally and as to the calcium content of the bones improved slowly until January, 1937. At this time he again began to experience some of his original complaints, such as weakness and pains in the muscles, and hoarseness increased. The blood calcium rose above the normal, and the blood phosphorus was lowered. No cause could be found for this until the middle of July, 1937, when an enlargement of a cervical gland on the left side of the neck was noticed.

This gland was removed at once and sent to the National Institute of Health for study. The report is as follows: "The 8 by 11 mm. tumor mass is enclosed in a dense layer of scar tissue, which is thicker where it gives rise to trabeculae which completely or incompletely lobulate the tumor. This fibrous tissue shows patches of lymphocytes and little scattered, free and phagocytosed hemosiderin.

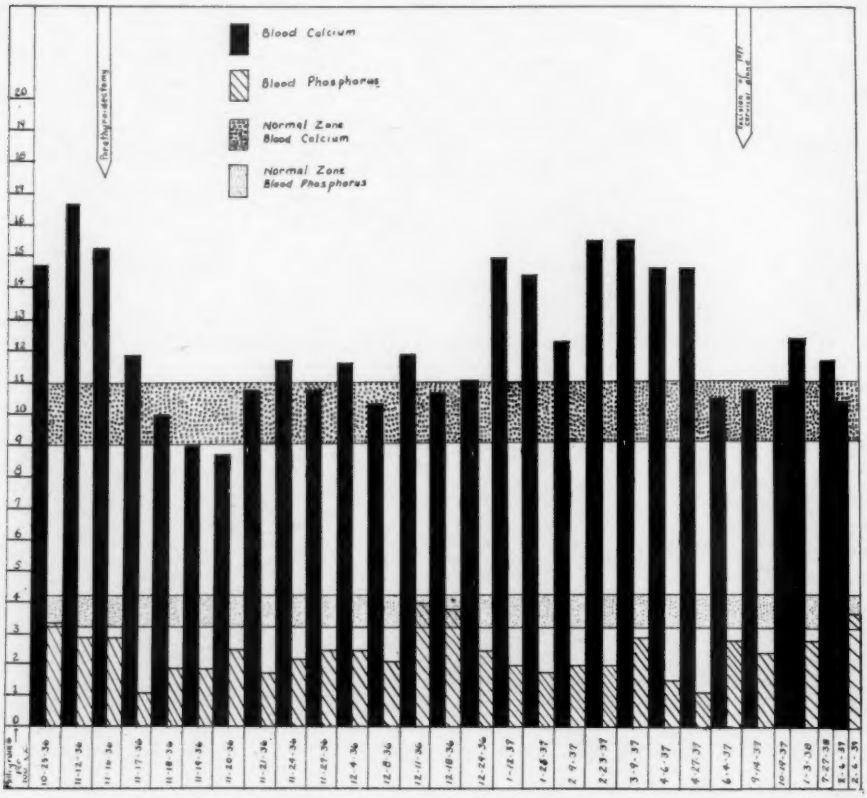


Fig. 9.—Blood calcium and phosphorus levels during course of two and one-half years' observation.

Parenchyma is formed of large and small sheets and strands of coherent tumor cells which are polygonal, medium to large in size, and have distinct cytoplasmic margins. Cell nuclei are medium to large in size, round, vesicular, and moderately hyperchromatic, and show one or more distinct, usually large nucleoli. Few mitoses are seen. Cell cytoplasm is ample, granular, and oxyphilic, less often amphophilic. Tumor cells immediately surrounding blood vessels are usually larger than elsewhere, are roughly columnar and show irregular radial arrangement. Few cell sheets show focal coagulation necrosis. A small collapsed cyst present in peripheral fibrous layer is lined by bud-like masses of vascular granulation tissue. In some of the vascular spaces, there are masses of tumor cells, some apparently lying free while others are loosely adherent to wall [Fig. 10]. In some of these vessels there is little blood. Occasionally a tumor mass occurs in a larger vessel.

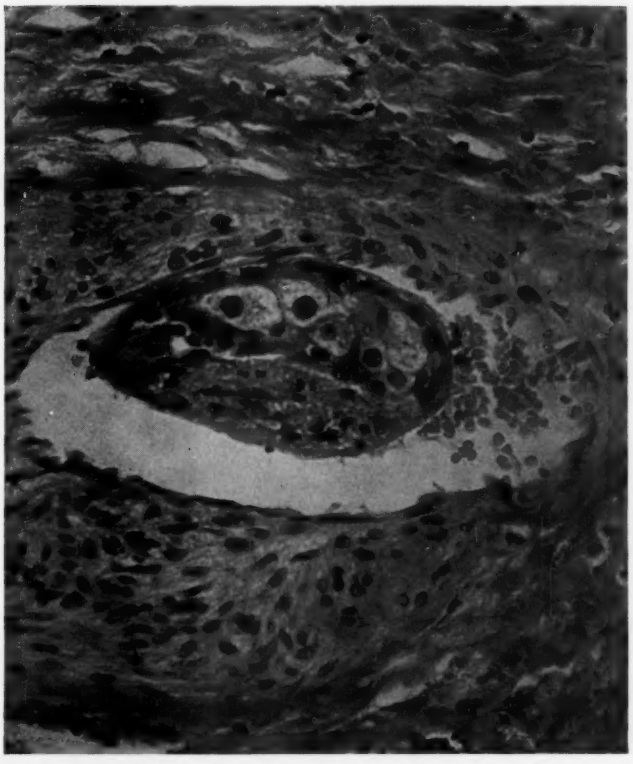

Fig. 10.—Section from metastasis to left cervical lymph node showing intravascular tumor mass (×515).

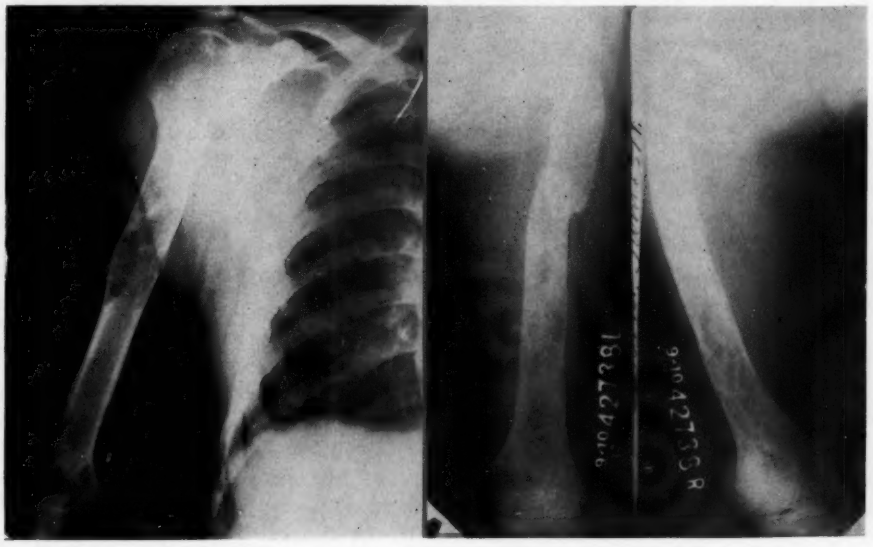

Fig. 11. Fig. 12.

Fig. 11.—Right humerus with fracture of surgical neck healed. Decalcification throughout bone is less marked (Sept. 10, 1937).

Fig. 12.—Right and left femurs with fractures healed. Density of bones increased (Sept. 10, 1937).

"A small lymph node loosely attached to tumor shows moderate sinus endothelial proliferation. A second detached node shows in addition a vascular space filled with tumor cells.

"Diagnosis: Malignant adenoma of parathyroid gland, metastatic."

After removal of the metastatic gland, the blood chemistry returned to normal levels (Fig. 9). The fractures healed rapidly, and some of the cystic areas of the bones became more densely filled with calcium (Figs. 11 and 12). The patient was discharged Nov. 1, 1937. At this time he was able to walk with crutches.

On Jan. 3, 1938, the patient was readmitted for check. His weight was 135 pounds. Clinically, union appeared firm at site of fractures; some deformity was present at the site of fractures; both knee joints were slightly swollen; urine showed 1 plus albumin; Kline exclusion test was negative. P. S. P. test showed 20 per cent function in fifteen minutes, 30 per cent in one hour. Blood calcium was 12.5 mg. per 100 c.c. of blood. Blood phosphorus was 2.7 mg. per 100 c.c. of blood. *X-ray Report:* "The cystic changes in the femurs are still quite noticeable but there is evidence of considerable recalcification present. The old fractures are firmly united and appear quite strong. There are no cystic changes in the fibula or tibia of either leg. The cystic changes in the humerus of each arm are quite outstanding. Almost the entire shaft of the humerus is involved. The middle third of the right humerus shows the greatest changes observed in that bone. The changes in the right humerus are less prominent now than previously. The left humerus does not show any improvement."

The patient was discharged on Jan. 15, 1938, to return in six months. Patient was readmitted July 27, 1938. His chief complaint was pain in his arm and inability to use his left arm. Otherwise, his general condition had been good since the last admission. He could use his right arm freely. His weight was 132¾ pounds. Blood pressure was 170/110. Physical examination was practically the same. Right knee at this time had considerable grating on movement; the motion of the left shoulder joint was limited in all directions and appeared to be tender over the middle portion of the humerus where there appeared to be fusiform swelling. Urine showed 3 plus albumin; Kline and Eagle tests negative; blood calcium, 11.7 mg. per 100 c.c. of blood. *X-ray Report, July 30, 1938:* "The left humerus, scapula and outer end of the left clavicle show the same general condition as was previously observed in November, 1937, except that the radiolucent areas are more clearly defined now and somewhat larger than they were at that time. There has been no suggestion of recalcification and there are new areas developed in the lower end of the humerus just above the epicondyle. The main shaft of the humerus is now little more than a shell of the normal bone. There is no break however in the external surface of the bone at any place. These changes were thought to be originally a result of a pathology of the parathyroid. In view of the malignant condition found in the adenoma removed from the region of the parathyroid and also since there had been no recalcification of the cystic-like areas found throughout the general skeleton, these changes are quite interesting and unusual. Biopsy should prove most interesting."

*X-ray Report on Aug. 2, 1938:* "The cystic areas in the femurs are not as prominent as when previously observed over a year ago [Fig. 13]. The tibias appear essentially normal. Each humerus shows gross cystic areas some of which are so great as to leave merely a shell of the bone shaft [Fig. 14]. The left is the greater involved and there are two new cystic areas in the lower section of the left humerus which has developed in the past year. These are quite circumscribed in outline. The bone changes in this case are most unusual, especially in view of the malignant nature of the tumor removed from the region of the parathyroid gland."

At this time, the patient was able to walk without the aid of crutches, hoarseness in his voice was improved, and his chief complaint was pain in the left shoulder

and arm. (No report of the phosphorus content of the blood at this time.) He was discharged on Aug. 8, 1938, to return in six months for check.

Patient was readmitted Feb. 6, 1939, for check. On this admission, he did not offer any complaint. His general appearance was good. His weight was 132 pounds and blood pressure was 185/108. On examination and special examination of the neck, there was no evidence of any local recurrence. His blood calcium was 10.5 mg. per 100 c.c. of blood and phosphorus was 3.7 mg. per 100 c.c. of blood. *X-ray Report:* "The femur shows all the old fractures firmly united and greater density than at previous examinations. The gross cystic changes previously observed in the humerus of each arm appear essentially the same. There are large cystic areas in the shaft of both bones. In some areas, there is little more than shell of the bone remaining. The fracture of the humerus is firmly united."

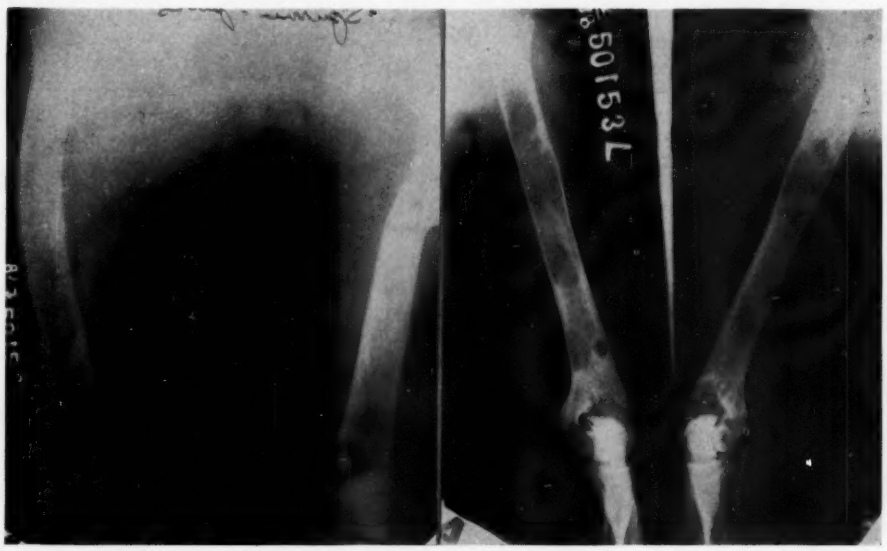

Fig. 13. Fig. 14.

Fig. 13.—Femurs well healed, twenty-two months after admission.

Fig. 14.—Right and left humerus twenty-two months after admission showing very little improvement in the right. Two new cystic areas are seen at the lower end of the left humerus.

## COMMENT

Including the case presented herein, there have been reported 22 cases of malignant tumors of the parathyroid glands. Nine of these have been in females and 12 in males. The sex of 1 patient was not noted. The youngest and oldest patients were 29 and 71 years of age, respectively. Three cases were patients between 29 and 45 years of age, and 17 were in patients from 45 to 71 years of age. Two reports omitted the age of the patients. The tumor was situated on the left side of the neck in 10 cases, on the right in 6, in the midline in 2, and in 4 the sites were not listed. The sizes of the tumors ranged from small nodular rests to 12 by 9 by 9 cm. In 4 cases bony decalcification was present. The favorite sites of metastasis were the muscles of the shoulder and neck, cervical lymph nodes, trachea, and lungs. Recurrence at the original site occurred in 2 instances.

Grossly, most of the tumors were densely covered by a thick fibrous connective tissue capsule which occasionally was densely adherent to contiguous muscle. Most of the tumors were nodular and lobulated. Their consistency varied greatly. Some were stony hard, some were firm but elastic and possessed fluctuant areas. Calcified areas were present in a few specimens. The color ranged from a bluish gray to reddish brown.

On cut sections, the tumors appeared yellowish gray, yellowish brown, or some intermediate color. From the capsule, trabeculae of fibrous connective tissue were found to course through the tumorous mass completely or incompletely to lobulate the neoplasm. In many specimens cystic areas with thin walls of fibrous connective tissue were noted. These cysts were filled with an amber-colored serous fluid or amber colloidlike material. Occasionally they contained blood. In 1 case the cyst was encircled completely by a ring of calcium deposit (Fig. 4), which was visible in an x-ray film taken before the tumor was removed from the patient (Fig. 2). In some nodules of the tumors, necrotic centers were found.

Microscopically, all the tumors reported exhibited definitely the structure of the parathyroid glands. The stroma was usually made up of thin connective tissue fibers. At times the supportive network consisted of thick fibrous bands with lymphocytic or lymphoidlike cell infiltration. Occasionally the stroma was formed almost completely by capillary vessels.

The parenchyma consisted of compact, anastomosing strands of cells in between which were found vesiclelike spaces, thereby giving the effect of palisades. Such order was not necessarily always present, as Guy[23] found the cells growing in "lawless profusion." Varying sizes of cell sheets or nests were seen which were or were not enclosed by fibrous tissue.

Although the individual cells were predominantly of the large, clear variety (principal cells), several cases showed a predominance of oxyphilic cells. Others possessed approximately equal numbers of each type. The boundaries of the cells were distinct, encircling an abundance of cytoplasm, which in the clear type was poorly stained. In the oxyphilic cells the cytoplasm was finely granular and moderately or markedly eosinophilic. Although the most predominant cell shape was polygonal, many were spheroidal or cuboidal. The nuclei were round or ovoid, usually centrally placed, either vesicular or homogeneous, and possessed a fairly abundant amount of chromatin material. Their size varied considerably, but usually they were very large. Wellbrock[21] found the largest nuclei to be approximately seven times the size of a normal nucleus. Usually they contained one or two fairly deeply staining nucleoli. The number of mitotic figures was not constant. In some cases they were seen only occasionally, while in others they were present abundantly.

In all cases in which metastases occurred, the metastatic growth showed the same histopathologic picture as the primary tumor, with a tendency to possess characteristics of a greater degree of malignancy. Additionally, as seen in our case, the metastasis is apparently quite capable of exerting the same influence on the metabolism of calcium as that held by the normal gland, but this influence is without restraint.

There are no definitely dependable characteristics by which a tumor of the parathyroids might be diagnosed clinically as benign or malignant. For the most part, malignant tumors are usually larger. Hall and Chaffin[27] in 1934 noted that over 50 per cent of the benign tumors recorded in literature had shown decalcification of the bones to some degree, while only demineralization had been seen in only 1 case[21] of the 18 malignant tumors which they had reviewed. They concluded, therefore, that bony changes were not so likely to be present in patients with parathyroid malignancies, and if they were, the chances of the tumor's being benign were considerably increased. With this report, 4 cases of malignancy of the parathyroid glands have been noted in which demineralization of the skeleton occurred.[21, 26, 28] In only 1 case[28] were the bony alterations described as a diffuse miliary osteoporosis. The other 3 possessed large cystic areas, particularly present in the long bones and pelvis. One should bear in mind that procrastination should not be courted in removing a parathyroid tumor because bony changes are present. It might still be a malignant affair!

## SUMMARY

1. A brief description of normal parathyroid glands is presented.

2. Twenty-one cases of malignant parathyroid tumors found in the literature are reviewed briefly.

3. An additional case of parathyroid malignancy is reported. The tumor was situated in the left side of the neck and metastasized to a left cervical lymph node. The cells comprising the neoplasm were of a variable large size, mostly polygonal, and contained oxyphilic cytoplasm. The vesicular nuclei were fairly large, moderately to markedly hyperchromatic, and contained one or two hyperchromatic nucleoli. Few mitoses were seen. The cells were arranged in sheets, nests, and columns enclosed by fibrous tissue.

4. Decalcification of the bones was present and so marked that multiple fractures were sustained by the patient from an otherwise insignificant fall.

5. Three years after removal of the original tumor, the patient is alive and well. The fractures are well healed and moderate recalcification of the bones has occurred.*

*Since this paper originally was written, the patient was seen again in September, 1941. At that time his general condition was excellent and he felt much better than at any time since his original hospital admission in October, 1936. His blood calcium was 10.8 mg., and blood phosphorus, 2.8 mg. per 100 c.c. of blood. X-rays of both humeri show that all of the cystic areas have nearly filled in with calcium.

The authors are indebted to Dr. J. H. R. Booth, U. S. Marine Hospital, Baltimore, Md., for his splendid cooperation in the roentgenologic work involved in the case reported.

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# FASCIAL RECONSTRUCTION OF THE TIBIAL COLLATERAL LIGAMENT

HENRY MILCH, M.D., NEW YORK, N. Y.
*(From the Hospital for Joint Diseases)*

THE FUNCTION of the knee joint is, to a large degree, determined by the anatomical integrity of its ligamentous apparatus. Because of this, considerable effort has been expended in an attempt to establish the exact significance of each of its component parts in the mechanism of the knee as a physiologic unit. Despite the extensive literature on this subject, opinion is far from being unanimous. This may be attributed to the fact that some of the conclusions have been gained from clinical observation, others from anatomical or experimental studies. Though this information cannot and should not be neglected, it must not be forgotten that such data may not be directly applicable to the problems presented by clinical surgery.

The primary interest of the orthopedic surgeon is not the didactic determination of the function of each of the ligaments, but rather the evaluation of their relative significance to the knee as a whole. Information on this question can best be obtained by a study of the results of surgical efforts at repair of damage to definitely determined ligamentous structures. From the fact that anatomically the crucial ligaments appeared to be most important, the earlier surgical efforts were expended on the repair of these structures. These early trials were only partly successful, and a marked step forward was made when the fascial reconstruction, originally devised by Grekow[2] and later elaborated by Hey Groves,[3] was introduced. But even this did not seem to give complete satisfaction until a procedure for the repair of the tibial collateral ligament was added.[4, 9] Since then a number of different methods of fascial repair of this ligament have been devised by Campbell, Carrel, Cubbins, and others.[1] An ever-growing experience seems to indicate that the repair of the tibial collateral ligament is the essential step in the operative correction of the instability which results from loss of the normal ligaments of the knee joint.

In an earlier communication[8] I expressed the opinion, concurred in by others, that injury to one or both of the crucial ligaments was not incompatible with good knee function, but that permanent damage to the tibial collateral was definitely disabling. The lapse of time has not altered this opinion. On the contrary, it has even led to the firm conviction that in the majority of cases injuries to the crucial ligaments cannot be diagnosed with any clinical assurance unless they are associated with injury to the tibial collateral ligament. The so-called

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"drawer" or "rocker" sign of De Rocher, which has been considered pathognomonic of crucial ligament injuries, has been elicited usually in those cases in which there has been concomitant injury to the collateral ligament and cannot commonly be elicited if this ligament be intact.

Where this sign has not been present, crucial ligament injuries frequently have led to transitory locking of the knee and have simulated the clinical picture of torn or displaced menisci. Under this mistaken diagnosis, arthrotomy of the knee has repeatedly been performed. In the first few cases in which only a tearing of the anterior crucial ligament was found, the extensive Hey Grove reconstruction operation did not seem warranted by the relatively minor clinical disability. Since the torn ligament appeared to be acting principally as a mechanical block, it was excised. The excellent recovery of these patients justified the procedure, and in consequence, the torn anterior, and occasionally even both torn crucial, ligaments, have been excised without any serious results in those cases in which no evidence of injury to the medial ligament could be elicited. Where both the crucial and collateral ligaments have been injured, repair of the tibial ligament alone has been sufficient to restore an excellent functional capacity to the unstable knee.

If cases in which successful reconstruction of the tibial collateral ligament alone be compared with similar cases in which both the crucial and tibial collateral ligaments were satisfactorily repaired, it will be found that the results, both anatomically and functionally considered, are quite similar. Complete restitution to the normal is an almost unattainable ideal. For the patient, and consequently for the surgeon, it is the functional rehabilitation and not the anatomical restoration that is of primary moment. In this respect the more complicated crucial ligament reconstruction does not seem to have justified itself, while the importance of the tibial collateral ligament repair cannot be denied. The reestablishment of the integrity of this ligament is fundamental if a successful outcome of the surgical procedure is to be expected.

In general, this opinion coincides with that of Mauck,[7] who described an operative procedure on the tibial collateral ligament which served "to remedy the instability of the knee, due to injuries of the internal, lateral, and crucial ligaments." This procedure is based on the belief "that the instability was due to laxity of the medial ligament, rather than to weakness of the structure, and if weakness existed, it was in that part of the ligament adjacent to the tibial head—that portion which was healed by fibrous tissue."

Though it is generally believed that the tibial attachment is the most frequent site of rupture, the evidence on this matter is by no means overwhelmingly convincing. Mauck expressed the opinion "that the application of force which abducts and externally rotates the tibia on

the femur, with the knee slightly flexed (the position in which most injuries to the medial collateral ligament take place) practically always tears the ligaments away from the head of the tibia and the anterior fibers of the ligament suffer the greatest damage.'' Jones and Lovett[5] state that ''clinically, it is the lower attachment of this ligament which usually gives way'' and that in a sprained knee ''the short, deep fibers of the ligament are injured most often at their attachment to the tibia.'' However, in the same discussion, they note that ''in connection with injuries to the internal, lateral ligament, it is not uncommon to meet with a sprain fracture, which occurs most often where the ligament is torn from the femur, carrying with it a small flake of bone. A similar fracture also occurs when the deep fibers are torn from the upper margin of the tibia.'' They observe further that ''when the leg was forcibly abducted on the cadaver, Tenney found that the internal lateral ligament tore away from its femoral attachment.''

Though no accurate estimate of the relative frequency of tearing of the collateral ligament at one or another part can be made, it seems to be incontrovertible that the ligament may and does tear at any point in its continuity. In this regard, the arthrographic observations of Lindblom[6] are extremely important. He observed a group of eighteen cases with recent lesions. ''Pararticular leakage through a capsular rupture was seen above the meniscus in three cases and below it in two cases. In all cases of leakage about the meniscus, a rupture was found at the superior attachment of the ligament.''

This contradiction in the observed results is one which can only be resolved by actual observation of the fact in living patients. Clinical experience would seem to indicate that though the medial ligament may tear away from its tibial attachment, this is not the invariable or necessary site of rupture. In those cases of lateral instability in which the roentgenogram discloses a fracture in the region of the femoral epicondyle, rupture at the femoral attachment of the medial collateral ligament is generally conceded. An increasing fund of information concerning sport accidents has established the fact that the sprained knee of the skier is so constantly associated with a tender area over the femoral attachment of the ligament that this point has been specifically designated the ''ski point.'' Among football players, too, this area of tenderness is characteristic and is considered as indicating a partial tear of the medial ligament. Unfortunately, actual observations as to the site of rupture of the collateral ligament are not as numerous as could be desired. In the fresh cases, surgical intervention is not justified because of the excellent results obtained by adequate, conservative therapy. In the older cases, it is only with difficulty that the site or even the probability of the rupture can be accurately determined because of scar tissue replacement. It is particularly in regard to this point that the following cases are of interest.

CASE 1.—A. C., colored female, aged 38 years, was admitted to the Hospital for Joint Diseases on Oct. 18, 1938. She stated that while roller skating three years before she had fallen on her flexed and internally twisted right leg. The knee became swollen and painful. Extension was not blocked, but flexion beyond 90° was limited by pain. The patient was advised to make hot applications to the knee and in the course of several weeks the swelling disappeared. She remained well until about three weeks before her admission, when she slipped and again injured her knee in the same manner as previously. One week later she fell upon her hyperflexed knee and came to the hospital, complaining of stiffness and pain. She noted that after her fall the knee felt unstable, and it was necessary to steady the knee with her hand while extending the leg. During the act of extension she noted a snapping sensation along the inner aspect of the knee.

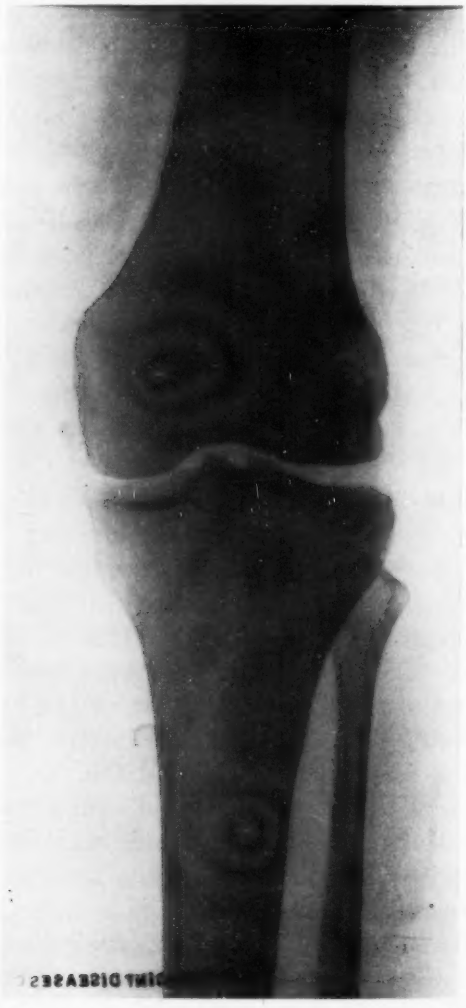

Fig. 1.—Roentgenogram showing nodule on inner aspect of knee.

Examination disclosed a marked swelling of the knee. There was a point of tenderness along the anterior margin of the medial collateral ligament, slightly above the level of the knee joint. This pain was markedly exacerbated by attempts at abduction of the leg on the thigh, but no abnormal lateral mobility could be elicited. The "rocker" sign was negative. Flexion could be performed to 45°. At this point the patient complained of increased pain. Extension was associated

with a clicking noise but was possible to 180° without locking. Roentgenogram (Fig. 1) was reported as showing a "cortical avulsion fracture of the internal femoral condyle, with separation of a small shell-like fragment of bone."

At operation, performed on Oct. 20, 1938, through an oblique incision, a typical bucket-handle fracture of the meniscus was found and the meniscus was removed. The bony body was then isolated. It was found to be about the size and shape of a grain of puffed rice, attached anteriorly to the articular aspect of the internal collateral ligament. There was apparently an articular facet. This mass was excised with uneventful recovery of the patient.

The pathologist reported that this nodule was a "flat, osseous fragment, with a narrow cartilaginous cap, which is found to be modified cartilage."

The fact that this small fragment of bone was attached to the anterior edge of the collateral ligament, with its modified cartilage facing into the joint, seems to indicate that the cartilage was not torn away from a previously existing articular surface but represented a metamorphosis of scar tissue under the stress of constant motion. The nature of the injury, the symptoms immediately noted, the concomitant cartilage injury, and the location of the bony nodule, all tend to confirm the belief that this mass represented the healing stage of a partial tear of the anterior portion of the ligament just above the joint line.

This was exactly the site of the rupture found in a patient upon whom the opportunity of operating within a week of his injury was offered.

CASE 2.—R. G., male, aged 25 years, was first seen on May 1, 1935, five days after he had injured his left knee by jumping over a hedge. He stated that in landing his left knee bent backward and sideway. Though he was "able to get up and walk about, his knee felt very weak and shaky." On walking, he noted that his knee locked and since that time it has repeatedly locked, with the knee in flexion. Examination disclosed that the knee could be extended to about 60° and flexed to 90°. There was marked effusion into the knee joint. There was definite tenderness over the femoral attachment of the tibial collateral ligament and over the fibular attachment of the fibular collateral ligament. In extension there was a marked increase in lateral mobility of the knee. Even when standing the patient was able to dislocate the femur backward on the tibia. In the seated position, with the knee flexed, there was a marked increase in anteroposterior mobility of the lower end of the femur. It was apparent that this patient had suffered a serious derangement of the ligamentous apparatus of the knee, involving both the crucial and collateral ligaments. Because of the symptom of locking, which was presumed to be due to concomitant injury of the semilunar cartilage, immediate operation was advised and performed on the following day.

At operation, a 3-inch medial parapatellar incision was made, and a large amount of bloody fluid was evacuated. The anterior horn of the internal semilunar cartilage was found detached and was removed. The medial semilunar fat pad, which was bruised and hemorrhagic, was removed. The anterior crucial ligament was found torn slightly above its tibial attachment. Since it could not be sutured, the free end was excised. Examination of the external semilunar cartilage revealed an injury to this structure. A small, lateral parapatellar incision was made, and a typical bucket-handle fracture of the external semilunar cartilage was found. The medial detached portion only was excised. Both synovial incisions were then closed,

and the knee was tested for lateral instability. Because of the marked hyperabductability of the knee, the tibial collateral ligament was exposed and carefully examined. A definite transverse tear below the femoral attachment of the tibial collateral ligament was found and was sutured with interrupted heavy chromic catgut stitches. As soon as this ligament was repaired, the abnormal lateral and *anteroposterior* mobility completely disappeared. The wound was closed in layers, and a plaster of Paris bandage was applied from the thigh to the toes, with the knee in complete extension and the foot in midposition. This plaster was left on for a period of six weeks, and after this physiotherapy was begun. Thereafter the patient left the city, but information from his family physician indicated that a satisfactory restoration of function had been obtained.

While it is true that the tibial collateral ligament may be purposely cut or accidentally injured and yet heal quite soundly, it must be admitted that such healing can only occur by scar tissue formation. It must also be admitted that where instability does occur, a relative lengthening of the ligament at the site of the scar tissue formation must be predicated. It is obvious then that a tear of the tibial collateral ligament at its femoral attachment must be repaired at this site, and a giving way of scar tissue situated in its midportion can be avoided only by a reparative procedure designed to reinforce this weakened area. If these observations be conceded, it becomes apparent that any operation designed to meet all of the contingencies must be one which restores the stabilizing function of the ligament as a whole. This conclusion applies with even greater force to those cases in which the integrity of the ligament has been lost in consequence of infection, arthroplastic or other surgical intervention. It was to meet these indications that the present procedure was evolved by modification of previously existing operations.

Experience with the older procedures has demonstrated that where the fascial graft is left attached at its femoral end, neither the exact course nor the requisite degree of tension can be obtained. Though a slight loss of tension may be compensated for by muscular action, the limitation of motion and the marked loss of tension which follow inaccurate placing of the graft are more serious and may vitiate the result.

Since the essential feature of the present procedure consists in the actual replacement of the tibial collateral ligament by a fascial graft, accurate information as to the exact anatomical attachment, direction, and action of this ligament is indispensable. If the normal internal lateral ligament is carefully examined, it will be found to present an entirely different appearance than is suggested by Gray's classical description. Instead of being a "broad, flat, membranous band," this ligament consists of two parts, anterior and posterior, each of which differs entirely in appearance and action from the other.

The main anterior part extends from the femur to the tibia in the form of a narrow, flattened, white band, almost tendinous, both in its texture and in its oval circumference. It is attached above on a ridge

of the tuberosity of the medial femoral condyle, just below the adductor tubercle. From here the ligament passes downward and slightly forward to its attachment on the tibia. The short, deep fibers to which the semilunar cartilage is fixed are inserted into the tibial tuberosity posteriorly along the line of the capsular attachment. The superficial fibers, about 10 cm. long, continue downward to about the level of the sartorious tendon, before being inserted into the tibia. A small bursa is interposed between the tendon and outer surface of the ligament.

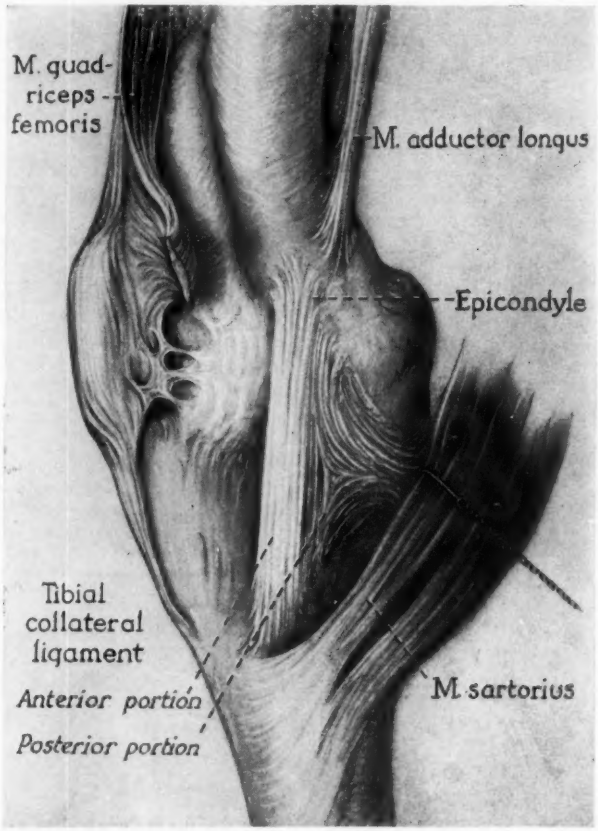


Fig. 2.—Drawing of lateral aspect of knee in extension, showing disposition of thick anterior portion of tibial collateral ligament and thinner posterior deltoid portion.

The posterior portion of the ligament is shorter and thinner than the anterior part. It is somewhat deltoid in outline, and its fibers radiate from the femoral and tibial origins of the main portion of the ligament to be inserted posteriorly on the medial fibrocartilage and the head of the tibia (Fig. 2).

Though the anterior and posterior portions are readily to be differentiated on their appearance alone, a more remarkable difference is noted on motion of the knee. The posterior portion of the ligaments becomes definitely taut in extension and markedly relaxed and redundant in flexion. *The anterior portion, on the contrary, remains taut*

*in all positions of the knee.* This is a noteworthy characteristic of the ligament, especially when consideration is given to the fact that the radius of curvature of the femoral condyle varies at different parts of its circumference. The fact that this portion of the ligament remains taut at all times is indicative both of the role it plays in maintaining the knee joint stability during all phases of its motion and of the necessity for restoring this tension in exactly the right plane if stability and unrestricted motion are to be obtained by any operative measure.*

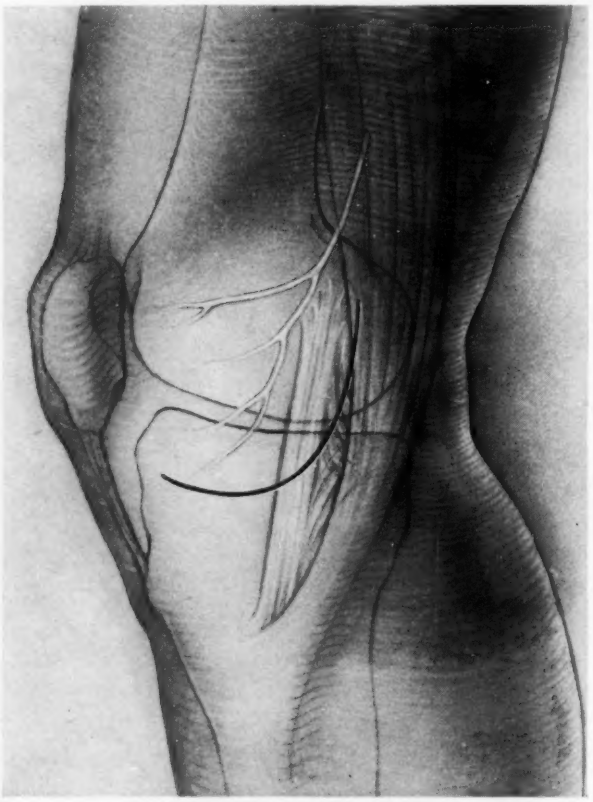

Fig. 3.—Transparent drawing showing relation of skin incision to bones and underlying soft tissues.

In its present form the operation is relatively simple. A curved L-shaped incision, about 6 inches long, is made on the anteromedial aspect of the knee joint (Fig. 3). The vertical arm of the incision begins just below the level of the adductor tubercle and is carried downward to about 1 inch below the level of the articular surface of the medial tibial tuberosity. At this level the horizontal arm of the incision is carried anteriorly toward, but not quite to, the edge of the patellar ligament. (This incision runs roughly parallel to the infrapatellar branch of the internal saphenous nerve, injury to which is avoided.) The skin flaps are dissected back. The deep fascia and the quadriceps

*Since the preparation of this paper, confirmation of these findings has appeared in a contribution by Brantigan and Voshell.[20]

expansion are incised in the same line as in the skin and reflected back as a separate layer. When this is finished, the tibial collateral ligament will be exposed in the posterior part of the incision. In the lower part of the wound, the anterior half of the medial meniscus will be seen extending from the anterior edge of the internal ligament forward to the patellar ligament. In this area the joint is opened and its medial half explored. The cartilage or crucial ligaments are treated, and the synovial membrane is again closed tightly.

The upper and lower attachments of the anterior portion of the tibial collateral ligament are now exposed and two drill holes are made at each end of the ligament by a ⅜ inch hand drill. The two upper drill holes are connected by a tunnel which passes transversely beneath the femoral attachment of the ligament, and the two lower drill holes are

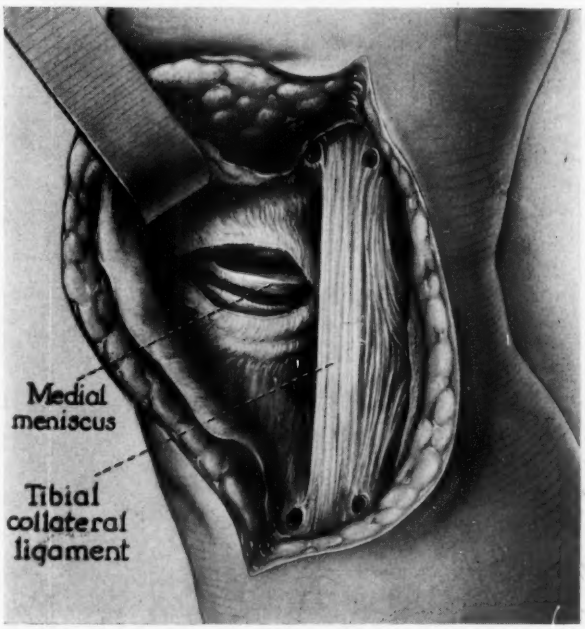


Fig. 4.—The joint is opened, exposing the semilunar cartilage. The drill holes in the bone for the fascial graft are shown.

similarly connected by a bone tunnel passing beneath the tibial attachment (Fig. 4). A piece of fascia 10 inches long and ½ inch wide is subcutaneously cut from the fascia lata of the same leg by means of a fascial stripper. The fascial graft is then passed in and out through the two upper drill holes, then down alongside of the tibial ligament, through the two lower drill holes, and back up to the origin. The leg is held in hyperadduction, and the remnants of the injured tibial ligament are sutured with several interrupted chromic stitches. This serves to maintain the leg in adduction on the femur and at the same time eliminates any tension on the graft during the period immediately following operation. The fascial graft is now sutured to the periosteum,

both at its entrance and exit, into the femoral drill holes. The graft is pulled down taut and again sutured at its entrance and exit from the tibial drill holes. The ascending limb of the graft is pulled taut and sutured to its free end. The medial collateral ligament is now outlined on four sides by a quadrilateral graft, the ascending and descending arms of which are visible, while the transverse arms are buried in the bone tunnels. The two vertical arms are next sutured to each other directly over the anterior part of the original collateral ligament so as to increase still further the tension under which they are placed (Fig. 5). The fascia and skin are then closed in layers with interrupted stitches, and a plaster of Paris bandage is applied, with the leg held in adduction. This is left on for a period of four to six weeks and is then removed and gentle active motion begun. Weight bearing may be begun at the end of six weeks, but as a matter of additional precaution, a knee cage brace should be supplied and the inner border of the shoe should be wedged to prevent excess tension on the new ligament.

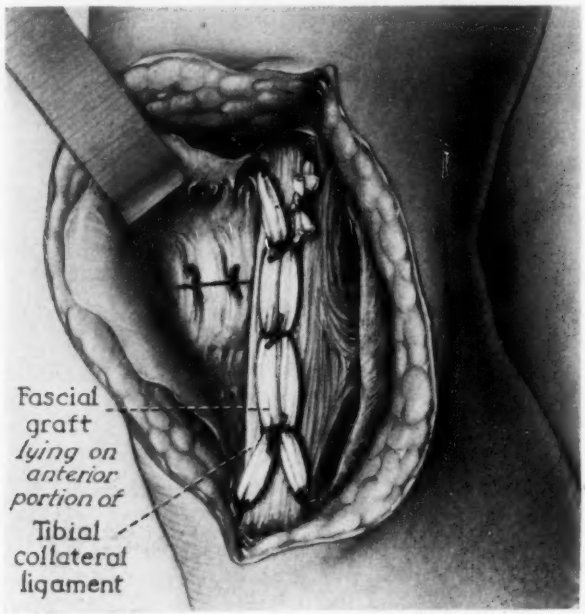


Fig. 5.—The joint is closed and the fascial suture is in place.

In conjunction with other operations, the principle of this operation has been employed in about a dozen cases. By itself the procedure has been employed in 6 patients, 4 being cases of traumatic rupture, 1 being a case in which the ligament proved insufficient after an arthroplasty of the knee, and 1 being of congenital anomaly. All these cases were operated upon with the knee in extension, and in 5 there was satisfactory re-establishment of lateral stability in extension. In 1 case there was a slight lateral mobility, which in extension did not exceed several degrees but which in flexion appeared to be somewhat greater.

Despite this the patients were well pleased with the functional result and were able to resume their normal pursuits with but slight inconvenience. It may be that this slight defect could be overcome by making the fascial graft taut with the knee in flexion. This point should be further investigated. In the 1 case in which the result was considered unsatisfactory, infection occurred and the fascial graft sloughed out of the wound.

### TRAUMATIC RUPTURE

*Satisfactory Results.—*

CASE 3.—B. G. was originally operated upon in February, 1934, after an injury to the left knee. At operation the anterior crucial ligament was found to be torn. The medial meniscus was fractured, and there was a marked laxity of the knee joint due to a concomitant injury to the medial collateral ligament. The cartilage was resected, and only the tibial collateral ligament was repaired in the manner previously described. The leg was encased in plaster for a period of six weeks, and thereafter gentle, active motion was begun. The patient was seen at intervals, the last being in January, 1938, at which time she had a completely stable knee, both in the anteroposterior and lateral planes, with normal, powerful extension of the knee joint and only the slightest degree of limitation of flexion. The patient complained of a slight sense of uncertainty in the knee, but she was able to engage in all of her usual activities without any limitation whatsoever.

CASE 4.—B. B., a markedly obese female, aged 45 years, was first seen in February, 1935, about one week after she had fallen down four steps, injuring her left knee. She stated the knee had turned under her in hyperflexion and abduction and after the accident she was unable to walk or bear weight upon the leg. The patient had to be taken home, and since then she had noted that whenever she attempted to stand upon her leg, the leg was unstable.

Examination disclosed moderate tenderness on pressure over the internal condyle and to a lesser extent over the external condyle of the tibia. Anteroposterior and lateral hypermobility were present. The left knee could only be flexed to about 15° beyond a right angle, at which point the patient complained of pain. X-ray of the left knee was reported as being radiographically negative. Operation was advised and performed on Feb. 28, 1935. At operation the medial half of the postpatellar fat pad was found to be contused. The posterior half of the internal semilunar cartilage was fractured. Both crucial ligaments were torn, the anterior at its midportion and the posterior slightly below its femoral insertion. The deep fibers of the internal lateral ligament were torn at their tibial attachment, and the ligament was definitely relaxed. The anterior crucial ligament was resected along with the internal semilunar cartilage. The posterior crucial ligament was sutured with chromic catgut. The internal lateral ligament was sutured and then reconstructed by a fascial graft in the manner described above. Complete immobilization of the knee by means of plaster was extremely difficult because of the patient's obesity. Nevertheless, fairly efficient adduction of the knee was maintained for a period of about six weeks, after which time the plaster was removed and exercises were commenced. The patient made an uneventful recovery with restoration of stability and functional capacity of the knee.

CASE 5.—G. G., male, 14 years of age, was first seen in the hospital on May 4, 1936. He stated that two and one-half years before he had been in an automobile accident in which he had suffered a fracture of the skull and contusion of the left knee. About one year later, while broad jumping, his knee gave way under him and

he fell. Although no swelling of the knee was noted at the time, the patient complained of a dull pain on the inner aspect of the left knee. He has had two other attacks of giving way of the knee, but there was no history of locking or clicking. The last attack occurred about three months before the examination.

Examination disclosed only slight tenderness over the internal collateral ligament and a marked degree of both anteroposterior and lateral hypermobility. On forcible abduction of the leg, a gap of about ¾ inch could be opened up between the tibial and the femoral condyles. X-ray showed a chip fracture on the inner aspect of the left tibia immediately below the proximal epiphyseal line. A diagnosis of a torn tibial collateral ligament was made, and operation was advised and performed on May 7, 1936.

At operation both crucial ligaments were found to be completely torn and were represented only by small stumps, which could not be sutured. The internal semilunar cartilage was removed, and a fascial plastic on the tibial collateral ligament was performed. Immediately after completion of the operation all anteroposterior mobility disappeared, leaving only a very slight amount of lateral mobility, which was corrected by reefing the medial half of the patellar retinaculum. After the usual period of immobilization in a plaster of Paris bandage, motion was started and gradually increased.

At examination on May 11, 1939, a matter of three years after operation, the patient had a completely normal range of flexion and extension. In extension there was the very slightest trace of lateral mobility noted, not exceeding 2 or 3°. Anteroposterior mobility was completely absent. The patient stated he was able to engage in all of his normal activities, although he occasionally complained of a slight sense of weakness in the knee.

### *Unsatisfactory Result.—*

CASE 6.—E. D., male, aged 30 years, was seen in January, 1939, following an injury about five weeks before in which he had slipped on a pile of old iron and twisted his left knee. Despite severe pain the patient continued at his work for that day, but on the following day he was unable to work because of swelling and inability to bend his knee. Under rest and hot applications the swelling disappeared, but the patient noted intermittent episodes of locking, clicking, and giving way of the knee. On crossing his knees he noted occasional clicking sensation in the joint.

Examination disclosed no fluid in the knee joint and no crepitus on motion. Powerful, active extension to 165° was possible. Passively, the knee could be extended to 180°. Flexion was normal. There appeared to be some tenderness over the anterior horn of the internal semilunar cartilage, with accentuation of the tenderness on extension of the leg. With the knee in extension about 15° of hyperabduction was possible and the joint could be opened sufficiently to see the outlines of both the femoral and tibial condyles beneath the skin along the inner aspect. In the flexed position there was a slight increase in anteroposterior mobility. There was marked tenderness over the tibial attachment of the tibial collateral ligament.

The x-ray showed a slight shadow in the region of the crucial spine but was otherwise negative. The patient was considered to be suffering from a tearing of the tibial collateral ligament, and operation was advised.

At operation, which was performed on Jan. 26, 1939, the tibial collateral ligament was found to be torn almost completely across at the level of the upper surface of the medial meniscus. It is to be noted, however, that this did not correspond with the area of tibial tenderness. Upon opening the knee joint, the medial meniscus was found to be torn across at its posterior portion. The crucial ligaments were apparently intact. A fascial plastic reconstruction was performed and after closure of the wound, a plaster of Paris bandage was applied, immobilizing the knee.

The patient developed a slight temperature, and on examination of the wound a low-grade infection was found. This persisted for several weeks with a necrosis of a considerable portion of the fascial graft. At the end of six weeks the plaster was removed and a knee-cage brace was supplied to the patient.

Examination in August, 1939, disclosed slight, but quite definite, lateral instability with the knee in extension. Flexion was limited at 110° and active extension was possible to 175°. The patient stated that though there was a marked improvement as compared with the condition before operation, he did not have the sense of complete security which had been expected. This case was considered extremely valuable. Though the result could at best be considered mediocre, it definitely established the fact that (1) the tibial reconstruction obviated the instability and (2) secondary infection, with necrosis of the fascial graft, resulted in partial recurrence of the instability.

### INSTABILITY FOLLOWING ARTHROPLASTY

#### *Satisfactory Result.—*

CASE 7.—J. LaF., female, aged 23 years, was first seen in the hospital in March, 1937, four and one-half years after an abortion, as a result of which the patient developed a septic infection of the right knee. The patient was under treatment for this infection for a period of about one year, after which time she was discharged from treatment with bony ankylosis of the knee in the position of flexion. For three years prior to her admission to the hospital she had had no signs of any acute inflammatory process and she applied for treatment for correction of the ankylosis.

Examination disclosed the knee fixed at an angle of 130°, and the x-ray showed this was due to bony ankylosis. On April 29, 1937, an arthroplasty of the knee was performed with excellent result. When examined in July, 1938, it was noted, however, that though the patient could flex the knee to 90° and extend it to 180°, there was marked lateral instability. The knee could be abducted to a distance of 10 to 15°, and the patient complained of a sense of insecurity. On July 21, 1938, a fascial reconstruction of the tibial collateral ligament was performed, and the leg was immobilized in plaster. After seven and one-half weeks the plaster was removed and motion begun. In September, 1938, it was noted that there was absolutely no lateral instability in the extended position and flexion was possible to 140°.

In November it was noted that the range of flexion had not been increased, and x-ray disclosed that this was due to a bony excrescence on the tibial surface, which was a consequence of the arthroplasty and had caused no interference with motion until the normal tension of the ligamentous apparatus had been restored by the operative reconstruction of the tibial collateral ligament. Despite this limitation of flexion, the patient expressed herself as being definitely satisfied with the result of the operation, since the pain in the knee previously noted had disappeared and she was able to walk about with stability. The advisability of a reoperation for the removal of the articular excrescence is still under consideration.

This case is of particular importance in justifying the procedure here suggested, since it is to be presumed that following the infection and the arthroplastic procedure, the tibial collateral ligament must have been largely destroyed. In cases such as this the necessity for reconstruction of a new ligament is, of course, beyond question.

### MULTIPLE CONGENITAL DEFORMITIES WITH RELAXATION OF TIBIAL COLLATERAL LIGAMENT

CASE 8.—R. H., female baby, aged 2 days, was brought to the Out-Patient Department on Feb. 3, 1933. The patient, the last of three children, was a breech

presentation and was delivered without instrumentation by podalic version. Immediately after birth marked bilateral clubfoot, right genu valgum, and left genu varum were observed (Fig. 6). Examination disclosed that in addition the child was suffering from a congenital dislocation of the left hip and congenital dislocation of the right patella.

Numerous procedures, both open and closed, were undertaken for the correction of the clubfeet and for the hip dislocation. Since they are not of primary interest to the present discussion, the details of these treatments may be omitted.

The right knee presented an interesting combination of bony and ligamentous anomalies. The leg could be abducted on the femur to about 35° from the normal position to which it could be passively brought back. Extension at the knee was possible to 180° and flexion was limited at 150°. The patella, obviously maldeveloped, was laterally displaced above the external femoral condyle and was clearly riding high above the normal level. In addition, the roentgenogram disclosed a flattening of the distal femoral epiphysis and a typical tibia valga.

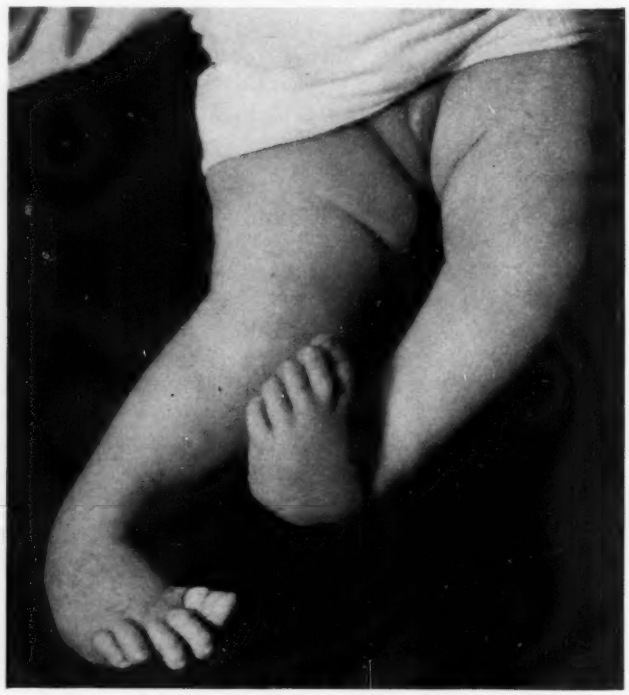

Fig. 6.—Photograph on admission showing deformities of feet and legs.

It was apparent that this knee was the locus of a number of different conditions, each of which required essentially different treatment. In the effort to correct the underlying bony abnormality, a plaster of Paris bandage was applied in 1934 and was gradually wedged to correct the tibia valga. Unfortunately, this had to be discontinued because of an inadvertent fracture of the lower end of the femur, which ultimately healed in fairly satisfactory position.

In 1936 the patient was admitted for osteotomy of the tibia. In 1938 the patient was admitted for treatment of the patellar dislocation and the limitation of knee flexion. The quadriceps tendon was lengthened by a Z-shaped incision. The knee was then completely flexed and numerous adhesions, both peri- and supraarticular, were disrupted. An elliptical flap of capsule was then removed from the inner aspect and transferred to the outer aspect of the knee joint capsule. The outer

long tongue of the Z-shaped tenotomy was then sutured to the inner long tongue and the wound closed. The knee was bandaged in flexion. Despite the routine slough of the overlying skin, the wound finally healed, and both active and passive motion was instituted. Ultimately, the patient was able actively to extend the knee to about 170° and to flex it to about 90°.

In the early part of 1940 the patient was again admitted to the hospital for the correction of the lateral hypermobility which still was possible to 30° from the midposition. The operation above described was performed on March 12, 1940, as a completely extra-articular procedure, since there was no need for exploration of the joint. On the operating table it was noted that immediately after reconstruction of the tibial collateral ligament, the lateral hypermobility was completely overcome, and the leg was held in a slightly bowlegged position. However, it was noted that passive flexion was limited at about 130°. The leg was immobilized in the usual manner and for the usual time. Following this, physiotherapy was instituted. In October, 1940, the range of flexion had increased to 115°, and this has since still further improved so that flexion is possible almost to a right angle. With the leg in flexion a few degrees of lateral mobility still exists, but in extension the stability of the knee is excellent. A slight genu valgum has recurred, but this is due to a flattening of the distal femoral epiphysis and will probably necessitate a later supracondylar osteotomy.

## SUMMARY

The surgical reconstruction of the tibial collateral ligament here presented has been employed since 1934. The satisfactory results from its successful restoration and the unsatisfactory result of the failure confirm the significance of the tibial collateral ligament in the function of the knee.

The procedure is completely extra-articular, though the approach is such as to permit ready access to the joint for exploration if deemed necessary. It is applicable to all relaxations of the tibial collateral ligament, regardless of the point at which rupture occurs. Since this ligament may tear at any portion of its continuity from the femoral origin to the tibial insertion, the method seems to possess special merit, particularly in those cases in which the site of rupture cannot be predetermined with accuracy. It is based on an anatomical conception of the tibial collateral which is different from that commonly accepted. It demonstrates that the only necessary element in the reconstruction is the accurate placing of the graft directly over the course of the anterior portion of the tibial collateral ligament.

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# A NEW CLAMP FOR ASEPTIC ANASTOMOSIS IN GASTROINTESTINAL SURGERY

MICHAEL DEBAKEY, M.D., NEW ORLEANS, LA.
*(From the Department of Surgery, Tulane University School of Medicine)*

THAT aseptic anastomosis in gastrointestinal surgery has long been considered a desideratum is readily evinced by the voluminous literature which has been amassed on this subject and the numerous ingenious instruments that have been devised for this purpose. However, in spite of these perennial contributions and reiterations of the obvious advantages of this method, the open anastomosis remains yet the most commonly employed procedure. It becomes obvious, therefore, that a satisfactory method of aseptic anastomosis has not been evolved. This has been due in great measure to certain objectionable features inherently present in practically all instruments utilized for this purpose. The instrument here to be described is presented with the belief that these difficulties and objections are obviated and the procedure can be performed with greater facility and simplicity.

The instrument consists of a strong crushing clamp similar in construction to the Rankin clamp[2] except for the absence of the middle blade (Fig. 1), two thin-bladed clamps, and a clamp holder (Fig. 2). The thin-bladed clamps consist of long, slender, narrow blades to permit the "turning in" of a minimum amount of bowel wall and have longitudinally grooved opposing surfaces to allow a firm grip. The open ends of the blades are so threaded that when the blades are approximated, a nut may be screwed on, thus locking the clamp in the closed position. To the hinged end of the blades is attached a pin which may be inserted into corresponding holes in both the crushing clamp and the clamp holder for securing the blades in the correct positions. The clamp holder consists of a handle with two parallel round holes at one end into which the pins of the thin-bladed clamp are fitted and secured.

The instrument may be used to perform aseptically various types of anastomoses, such as end-to-end, side-to-side, or end-to-side, following gastric or intestinal resections, as well as the closure of a blind end of bowel. However, for purposes of expediency, only one type, an end-to-end anastomosis, will be described.

The thin-bladed clamp is fitted into the large crushing clamp, secured in place by tightening the wing nut, and the blades opened widely (Fig. 3). The bowel, which previously has been appropriately prepared for resection, is placed between the blades at the desired site of division and crushed (Fig. 4*a*). The nut is screwed on the ends of the thin-bladed clamp and the crushing clamp opened and removed, leaving the crushed

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bowel wall firmly held within the slender blades of the thin-bladed clamp (Fig. 4*b*). Thus, it may be readily observed that the purpose of the heavy crushing clamp with the thick strong blades is to transmit the crushing force which could not be obtained by the thin slender blades. However, once the bowel wall is crushed, the thin blades are sufficiently strong to hold securely the coapted surfaces. An Ochsner or Payr clamp is applied immediately adjacent to the thin-bladed clamp and the bowel divided between them with the cautery (Fig. 5*a*). This procedure is repeated at the other end of the intended site of division and the resected

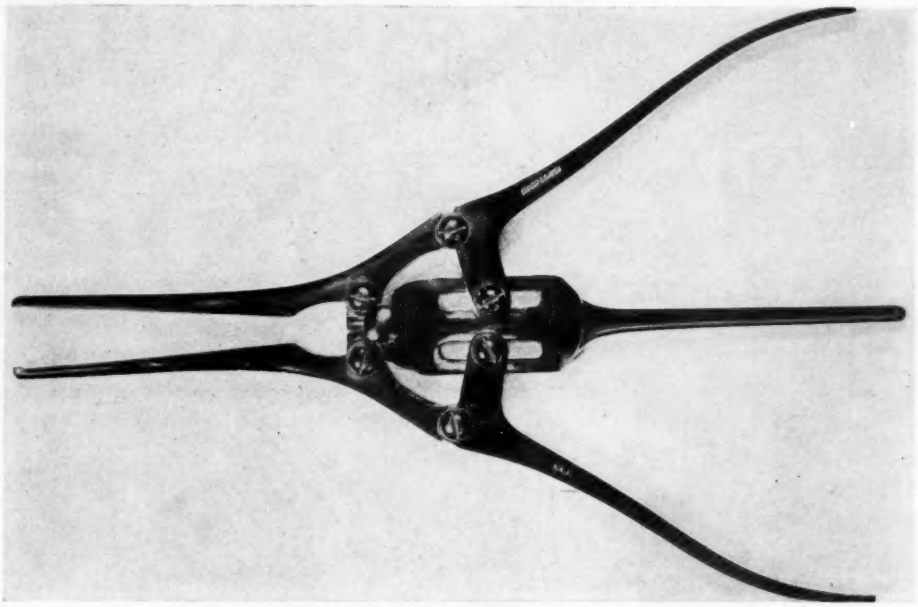

Fig. 1.—Photograph of the strong crushing clamp.

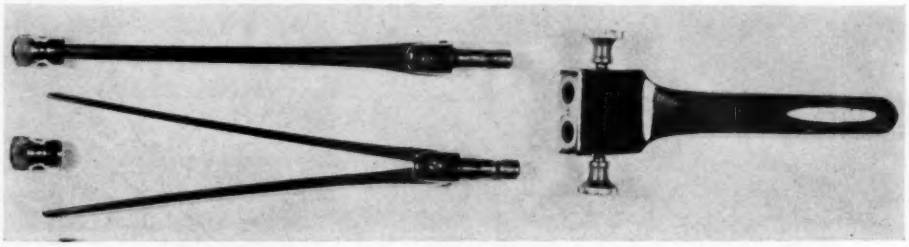

Fig. 2.—Photograph of thin-bladed clamps and clamp holder.

bowel included between the Ochsner and Payr clamps removed. Thus, it is observed that the large crushing clamp remains sterile because it is always removed before the bowel is divided. In this way only one large crushing clamp is necessary, although several thin-bladed clamps may be utilized in the operation. The thin-bladed clamps containing the proximal and distal ends of the bowel are then placed in the clamp holder by inserting the pins at the hinged ends into their respective holes in the clamp holder. The blades are then rotated, one clockwise and the other

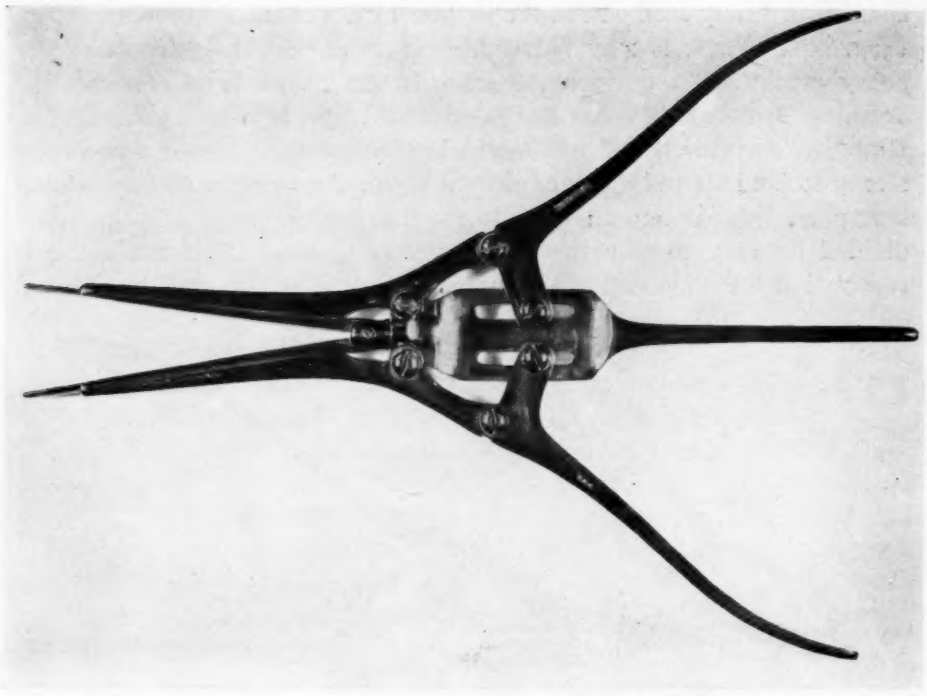

Fig. 3.—Photograph of crushing clamp with thin-bladed clamp secured in place.

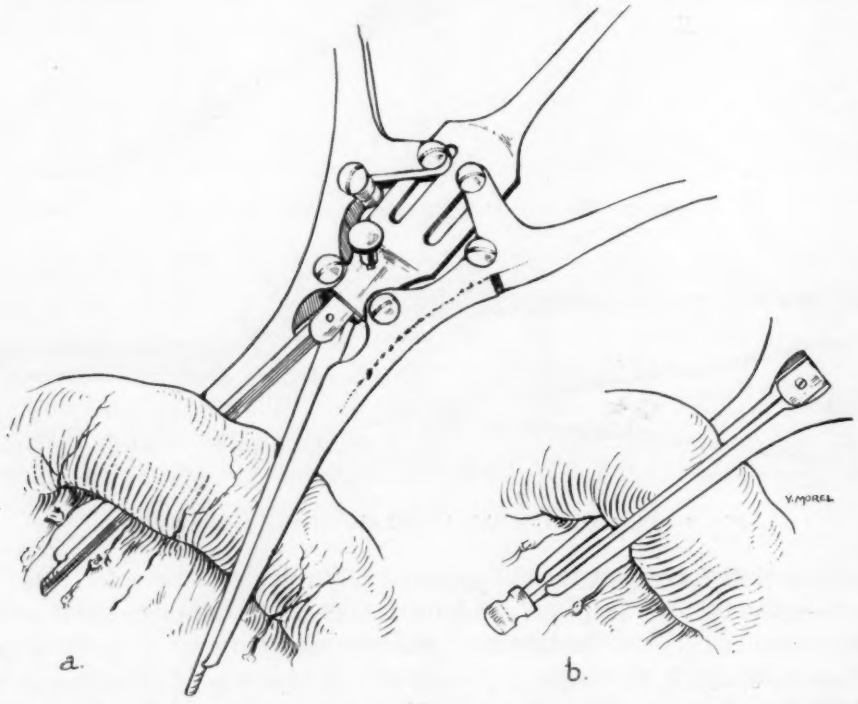


Fig. 4.—Drawing showing use of clamp in end-to-end anastomosis following resection of segment of bowel: (*a*) The bowel, which previously has been appropriately prepared for resection, is placed between the blades at the desired site and crushed. (*b*) The nut is screwed on the ends of the thin-bladed clamp and the crushing clamp opened and removed.

counterclockwise, in their longitudinal axis, so that the posterior wall of the respective ends of the bowel approximate each other more closely during the installation of the posterior row of sutures (Fig. 5*b*). The clamps are held firmly in this position by tightening the wing nuts against the pins in the clamp holder. Attention is directed to the necessity of placing the bowel at the intended sites of division in symmetrical portions of each clamp. This is considerably facilitated by the fact that the thin-bladed clamps are graduated in centimeters. In this way

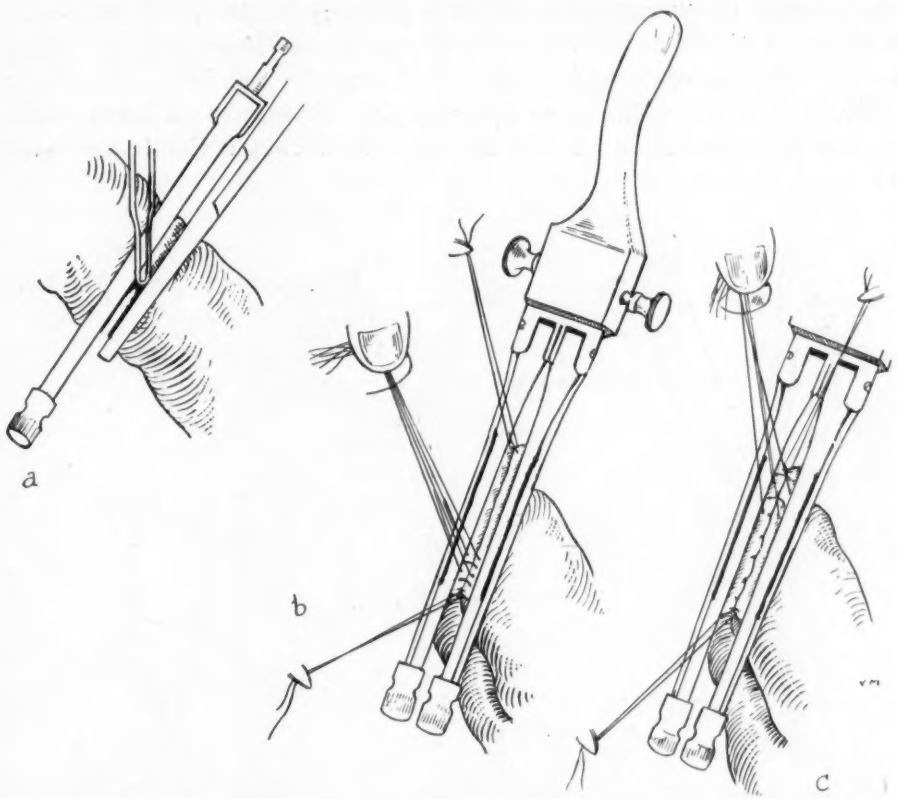


Fig. 5.—(*a*) An Ochsner clamp is applied immediately adjacent to the thin-bladed clamp and the bowel divided between them with the cautery. (*b*) After repeating the procedure illustrated in Figs. 4 and 5*a*, the thin-bladed clamps containing the proximal and distal ends of the bowel are placed in the clamp holder by inserting the pins at the hinged ends into their respective holes in the clamp holder and rotated and adjusted so that the posterior wall of the respective ends of the bowel approximate each other. The clamps are held firmly in this position by tightening the wing nuts against the pins in the clamp holder. The first posterior row of sutures is installed by using interrupted Cushing stitches of quilting cotton. (*c*) These sutures have been tied and severed, and a second row is similarly installed nearer the edges of the blades.

the proximal and distal ends of the bowel lie exactly opposite each other when the clamps are placed in the clamp holder. However, some adjustment can be made by inserting the pins of each clamp to the desired depth for accurate approximation of the respective ends of the bowel. The first posterior row of sutures is installed by using interrupted Cushing stitches of quilting cotton[1] (Fig. 5*b*). These sutures are tightened, tied, and severed and a second posterior row similarly installed nearer the edges of the blades (Fig. 5*c*).

The wing nuts are loosened, permitting rotation of the clamps toward each other, and the second posterior row of sutures tied and severed. The clamps are rotated a little more toward each other and the wing nuts of the holder tightened. The first anterior row of sutures is installed, using interrupted Cushing stitches of quilting cotton (Fig. 6*a*). The lock nut on the end of each clamp is unscrewed, permitting the blades to open, and as the clamps are removed, the sutures are tightened, thus approximating the bowel edges (Fig. 6*b*). After these sutures are tied and severed, the second anterior row is similarly installed and additional sutures are placed at the ends through which the blades projected, thus completing the anastomosis except for closing the rent in the mesentery (Fig. 6*c*). The crushed ends are opened by manipulation between the thumb and forefinger of the anastomosis through the bowel wall (Fig. 6*d*).

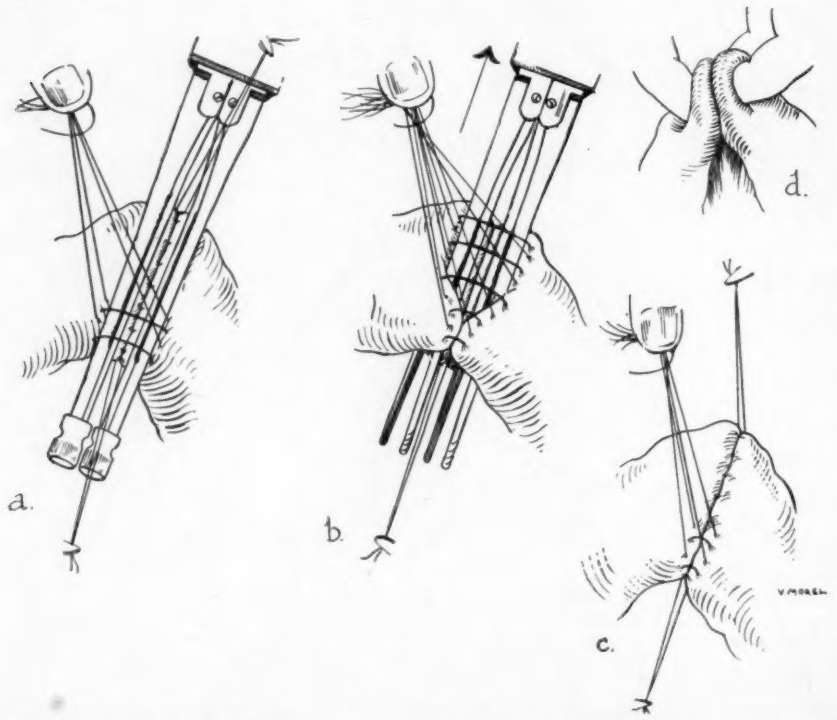


Fig. 6.—(*a*) The wing nuts have been loosened, permitting rotation of the clamps toward each other, and the first anterior row of sutures is installed, using interrupted Cushing stitches of quilting cotton. (*b*) The lock nut on the end of each clamp is unscrewed, permitting the blades to open, and as the clamps are removed, the sutures are tightened, thus approximating the bowel edges. (*c*) The sutures of the first anterior row have been tied and severed, and a second row is similarly installed and additional sutures placed at the ends and in the rent in the mesentery, thus completing the anastomosis. (*d*) The crushed ends are opened by manipulation between the thumb and forefinger of the anastomosis through the bowel wall.

The instrument was first tried on fresh autopsy specimens and its efficacy demonstrated. It was then used on the Tulane Surgical Service for the performance of various types of anastomoses. The simplicity and facility of performing aseptic anastomoses with this instrument in gastrointestinal surgery have been definitely established. The signifi-

cance of aseptic gastric resection has been recently emphasized by Wangensteen[3] and this instrument is readily adaptable to this procedure, although another size clamp having longer blades is necessary.

The obvious advantages of this instrument* are numerous. It permits a safe, simple, effective, and easily performed aseptic anastomosis. Because of the thin, slender blades of the clamp, a very small amount of bowel wall is turned in. The installation of the anastomotic sutures is considerably facilitated by the stable manner in which the bowel is maintained by the clamp holder, thus minimizing trauma of manipulation and obviating the necessity of other hands in the field. Moreover, because the posterior rows of anastomotic sutures can be placed just as readily as the anterior from the same position, turning the bowel ends over is unnecessary. This is a real advantage in certain types of anastomoses because of the awkwardness and difficulty which may be encountered in completing the posterior rows of sutures. Since only one large crushing clamp is necessary, the original cost and maintenance of the instrument are kept at a minimum.

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*The instrument has been manufactured through the courtesy of A. S. Aloe and Co., St. Louis, Mo.

# AN IMPROVED COLOSTOMY OUTFIT

GEORGE F. ARCHER, M.D., AND JULIAN G. RILEY, M.D.,
ATLANTA, GA.

A PERMANENT colostomy is an unfortunate handicap; about this there can be no argument. But it very definitely is not the intolerable thing that it has been considered in the past. With the proper management it is possible for a patient with a permanent colostomy to lead an approximately normal life.

The successful management of a colostomy depends on several things. First, the exact nature of the colostomy, its location, how much prolapse is present, and the direction in which its opening points. It is much easier for a patient to keep himself clean if his colostomy points downward and medially. Second, the intelligence and cleanliness which the patient displays in the care of his colostomy. And third, the type of colostomy outfit which he employs.

Ideally a colostomy should be so trained that it performs its function only at a given time each day. Since this, for practical purposes, is impossible, a colostomy bag or pouch is at present a necessary evil. The outfit employed should be of such a nature that it can be worn comfortably, that it requires little attention from the patient, and that it can be kept so clean that it is not surrounded by the disagreeable odor which all too frequently envelopes colostomy patients.

Many colostomy outfits have been devised but none of these has proved entirely satisfactory. The one about to be described was designed by a patient, Mr. C. D. Graves. It more nearly approaches an entirely satisfactory colostomy outfit than any other we have had occasion to see. For this reason we feel that it should be brought to the attention of the medical profession.

Fifteen years ago, following a two-stage operation performed by William Mayo for carcinoma of the rectum, Mr. Graves was left with a permanent colostomy. A colostomy bag was recommended for his use but did not function satisfactorily enough to permit the mingling with other people required by Mr. Graves' profession. Several other types of colostomy bags were investigated but seemed to offer no advantage over the one he had been wearing. Mr. Graves, being an intelligent and resourceful man, then began to experiment on himself with various homemade colostomy outfits. After fourteen years of self-experimentation he has gradually developed his present colostomy bag-tank which he now wears and feels to be highly satisfactory.

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Mr. Graves' colostomy outfit is composed of the following parts:

1. A washer, worn against the abdominal wall; this is a wax-coated, thin, flat, rubber washer with a flared inner edge. One rim of the washer is cut, allowing the ends to be overlapped, stitched together, and made to fit snugly around the individual colostomy. Extra washers of varied sizes are available.

2. The colostomy tank; this is made of wax-coated rubber stretched over a metal rim. A hole about one and one-half inches in diameter placed near one edge of the tank receives the colostomy stoma.

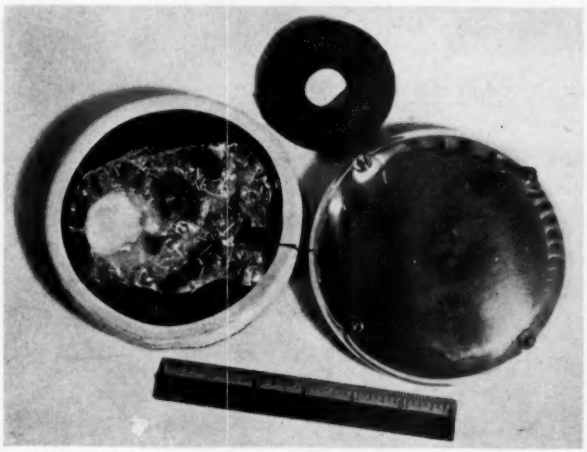


Fig. 1.

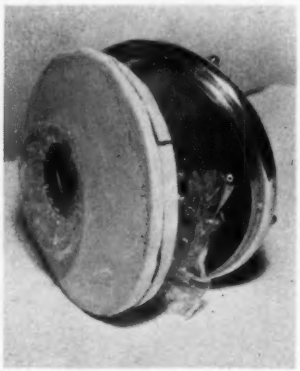


Fig. 2.

Fig. 1.—The unassembled colostomy outfit; rubber washer, cellophane bag, colostomy tank, and aluminum front.

Fig. 2.—Shows how the neck of the bag is drawn through the back of the tank and how the aluminum front fits in place.

3. Cellophane bags one-half or one pound size; these may be procured from any ten-cent store. The mouth of the paper bag protrudes through the hole in the back of the tank and is held snugly between the tank and the rubber washer.

4. The aluminum front of the tank; this fits snugly into the tank and the entire outfit is held in place by two elastic belts that snap onto the tank front. The tank front can be obtained in either of two sizes. The thinner of these has a depth of slightly less than one inch and can be worn when inconspicuousness is essential.

The wax used to coat the washers and the tank (except the aluminum front) is gulf wax. It can be bought at any ten-cent or grocery store. Its melting point is such that at body temperature it is soft enough to form a snug pliable junction. It permits the parts of the colostomy outfit to be cleaned and does not retain a fecal odor. Each time the bowels move, the cellophane bag is discarded, the washer rinsed with water and dried, and a new bag inserted in the tank.

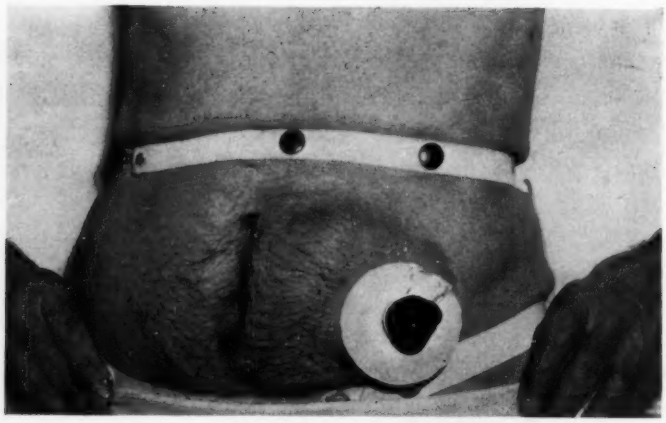


Fig. 3.—First stage in putting on the colostomy outfit. The belts are in place and the washer has been slipped over the colostomy stoma.

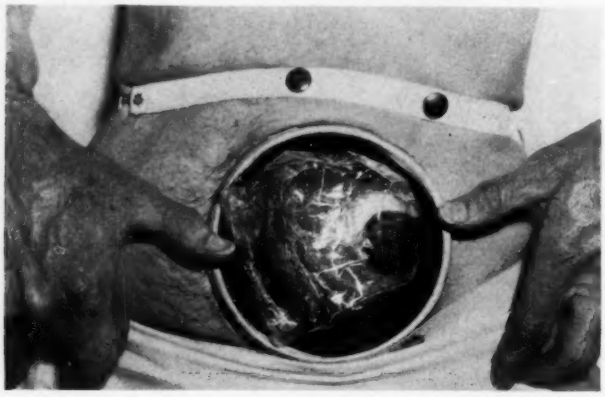


Fig. 4.—Second stage: The tank proper with its reservoir bag has been placed over the colostomy stoma and lies against the washer and the abdominal wall.

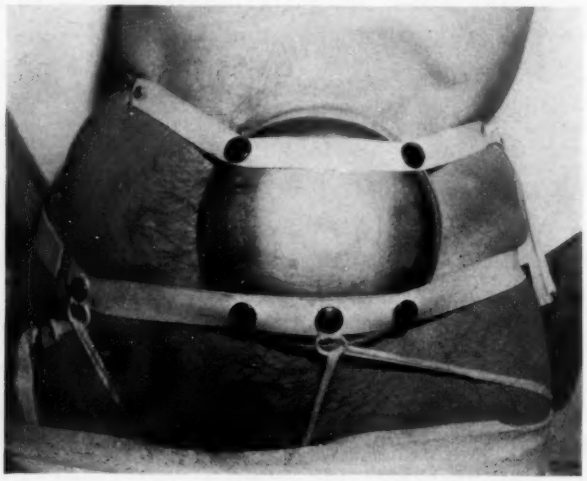


Fig. 5.—Third stage: The aluminum front has been applied to the tank and the entire outfit is held in place by two elastic belts.

Several advantages of this colostomy outfit are immediately apparent. Most important, the paper bags in which the fecal material is collected are easily and inexpensively obtained from any ten-cent store. They can, with a minimum contamination of the fingers, be removed, discarded in a water closet, and replaced. It is possible for the wearer to continue at his work even with a severe diarrhea. The use of two paper bags, one within the other, is said to keep at a minimum the odor from escaping colostomy gas. Wax-coated rubber is more easily cleaned than rubber not so coated and will not retain the odor of feces. A new coating of wax is easily applied by immersing, for a moment, the washer and tank in melted wax. Should the wearer of a bag-tank be caught in an afternoon subway rush, he need have no fear that a jostling crowd might cause him to soil himself. The tank protects him against blows and the belts hold it securely in place.*

During fifteen years of colostomy life, Mr. Graves has developed several little tricks which make easier the management of his colostomy. While taking a bath, he effectively closes his colostomy by tying it loosely with a single overhand knot of cotton rope. The piece of rope used is eight to nine inches long and is made by rolling between the hands B. & B. cotton, cut one-half inch wide with the fiber. Such a piece of cotton rope has enough tensile strength to close the colostomy but will not injure the bowel wall. It can be used again and again. In cleaning a soiled colostomy, it is important that the material used shall not be irritating to the mucous membrane. Wet kleenex or a wet soft toilet tissue, such as scot tissue, serves very well for this purpose.

We do not claim that this colostomy outfit is any panacea for all the troubles of a colostomy patient. There will be times when any such patient will soil himself in spite of all that he can do. However, we do feel that Mr. Graves' colostomy outfit represents a definite advance in the successful care of a permanent colostomy.

*Made by Mr. C. D. Graves, Dublin, Ga.

# Recent Advances in Surgery

CONDUCTED BY ALFRED BLALOCK, M.D.

## RECENT PROGRESS IN THE SURGICAL TREATMENT OF LUNG TUMORS

W. E. ADAMS, M.D., CHICAGO, ILL.

*(From the Department of Surgery of the University of Chicago)*

CURATIVE surgical treatment of primary lung tumors has been one of the most recent accomplishments in the field of thoracic surgery. Although rapid progress has been made by this specialty since World War I of 1914 to 1918 little success attended the treatment of lung tumors until within the past decade. As noted by Churchill[1] in 1933, articles and monographs dealt with all aspects of the subject except treatment which was "either not mentioned at all, or dismissed as was the March Hare's wine—'There isn't any.'" This view was substantiated by Carlson and Ballon[2] (1933), who in an exhaustive review of the literature were able to find only one patient surviving five years,[3] and another three years after resection (lobectomy). All others expired within two years or less of metastases or of local recurrence.

Thoracic surgery in general has lagged far behind abdominal surgery in its development, although Gluck[4] stated that surgery of the lung followed the rule of general surgery: *"Ubi haemorrhagia ibi ligatura, ubi tumor ibi exterpatio, ubi pus ibi incisio."* Réclus,[5] in an address at the French Surgical Congress in 1895, disagreed with Gluck, stating that "the structure of the lung and its air passages, the part it plays in sustaining the life of the blood, its relations with the heart and the presence of a pleural cavity all forbid great expectations and limit the power of the surgeon. Resection of a part of the lung for primary malignant disease is not even worth discussing. An accessible, single circumscribed growth would be a clinical wonder that would evade our present powers of observation." Subsequent events have substantiated Gluck's, rather than Réclus', point of view, when certain principles particularly applicable to the thorax are observed. That success was not forthcoming in the case of lung tumors until within recent years is difficult to understand.

S. Paget,[6] one of the foremost men in this field of his time, published the first comprehensive work on thoracic surgery in 1896. His book was occupied chiefly with traumatic wounds of the chest, infections and tumors of the chest wall, and empyema. Of the 462 pages,

less than 10 were devoted to intrathoracic malignant tumors and these were concerned chiefly with case reports. His prediction for the future could not have been farther from the truth when he stated: "It is sometimes said that surgeons fifty years hence will think as little of our results as we think of the methods of fifty years ago. So far as regards the surgery of the chest, this is utterly untrue. Fifty years ago it had risen above the horizon. It is now nearly at its zenith."

A careful survey of the factors involved which have delayed the successful surgical management of lung tumors enables one to group them under three headings: (1) altered cardiorespiratory function due to disturbance of intrathoracic pressures, (2) methods of diagnosis, and (3) resection of pulmonary tissue.

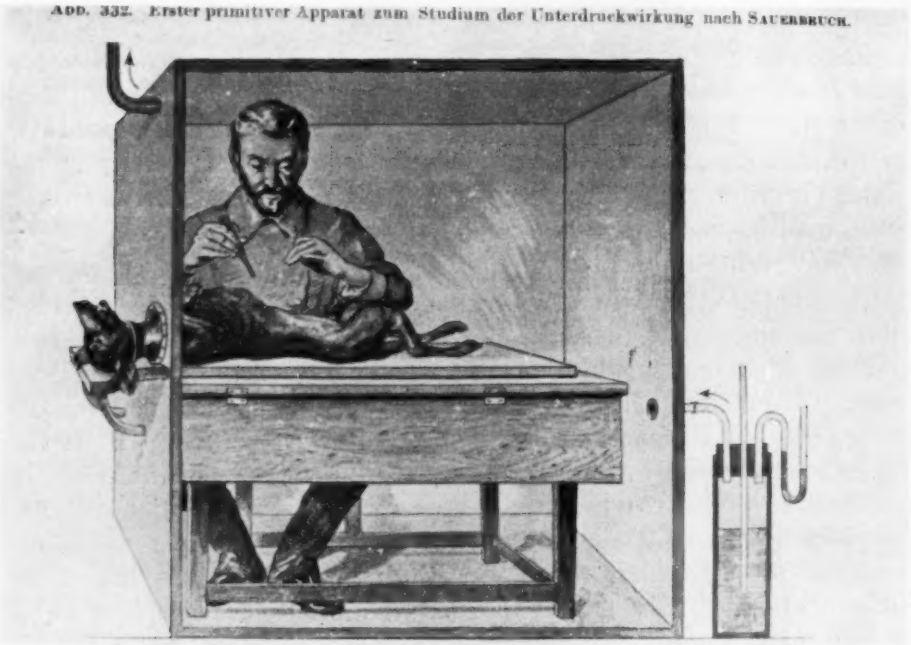
## PHYSIOLOGIC CONSIDERATIONS

One of the major factors which retarded intrathoracic surgery was the fear of an open pneumothorax. The dangers associated with this condition were recognized by the ancient Greeks, but they understood little of the underlying principles on which this was based. As early as the sixteenth century, however, some knowledge of the influence of altered intrathoracic pressures on cardiorespiratory function was gained from animal experimentation.

The anatomist at Padua, Vesalius,[7] demonstrated the dangers of an open pneumothorax to his students. He exposed the transparent parietal pleura, through which the movements of the lung could be seen. On breaking this membrane the lung would fall away from the side wall, but the motion of the chest remained unchanged. If the other pleural cavity was opened, "the lungs are seen as the result of perforation to fall together and collapse. The cardiac motion may not be observed for long, since suffocation of the animal will come on account of the collapse of the lungs. In order to restore the life of the animal, an opening is made in the upper part of the trachea, into which a pipe made from a reed is introduced and when it is broken into, if the lung rises up, the animal receives air. The lung should be inflated to the degree to which it occupied the thorax in life. The heart now gathers strength and its motion will change beautifully. Therefore, by maintaining repeated inflation of the lung, you may have opportunity to examine the motion of the heart both by touch and sight as much as you desire."

Thus we see that Vesalius understood both the untoward effects upon the cardiorespiratory function of open pneumothorax with its alterations of intrathoracic pressures, and a means of avoiding these deleterious effects or of overcoming them once they were established. For centuries, the dangers of an open pneumothorax were remembered, but the principle involved in the method of overcoming or obviating them was forgotten, or at least it was not associated with thoracic problems.

Methods, procedures, and even principles seem to have a way of being reborn or discovered again and again and so it was with the present principle involved. Von Mikulicz[8] set Sauerbruch[9] to work upon the problem of intrathoracic surgery and as a result the negative pressure room was constructed. Shortly thereafter, the positive pressure method of maintenance of expansion of the lung was elaborated upon and perfected by Meltzer and Auer.[10] The principle involved, i.e., maintenance of lung inflation, was the same with both types of pressure, one working from within the air passages and the other from without. The method of Meltzer and Auer which made use of intratrachial anesthesia under positive pressure had considerable advantage over that of the negative pressure chamber in that it was much less expensive, much simpler of operation, and, therefore, lent itself for a wider usage. In spite of



ADD. 332. Erster primitiver Apparat zum Studium der Unterdruckwirkung nach SAUERBRUCH.

Fig. 1.—Negative pressure room developed by Sauerbruch for intrathoracic operations on animals. A similar room was constructed for clinical use. (After Sauerbruch.)

Meltzer's work and Elsberg's[11, 12] application of the same to clinical surgery, a state of confusion continued to exist regarding the detrimental effects of an open pneumothorax. During the flu epidemic of 1918 empyemas complicating the influenzal pneumonias were accompanied by an extremely high mortality when treated by early open drainage. The work of Graham and Bell[13] of the Empyema Commission of the U. S. Army presented seemingly irrefutable evidence that the risk of an open pneumothorax was directly proportional to the size of the opening in the chest wall. Sauerbruch,[14] of Germany, was a staunch believer of this point of view. On the other hand, Duval[15] in France felt that these dangers had been very much exaggerated. Clinical evidence in support of

Duval's opinion is found in the use of spinal anesthesia for a considerable number of thoracotomies, notably in Canada and in England, without serious deleterious effects. As stated by Edwards,[16] "when the chest is widely opened and the lung is free from adhesions and collapsed, a patient under spinal anesthesia, i.e., at complete rest, is able to breathe comfortably and easily. If, however, cough occurs, there is invariably some respiratory distress which, if minimal, will settle in a moment or two, but if more severe, can only be controlled by the administration of a little oxygen given under slight positive pressure with a firm-fitting face piece." Why there exists the discrepancy between different patients under similar circumstances is not entirely clear. However, one fact is definitely understood; namely, coughing is not well tolerated during the presence of open pneumothorax without some

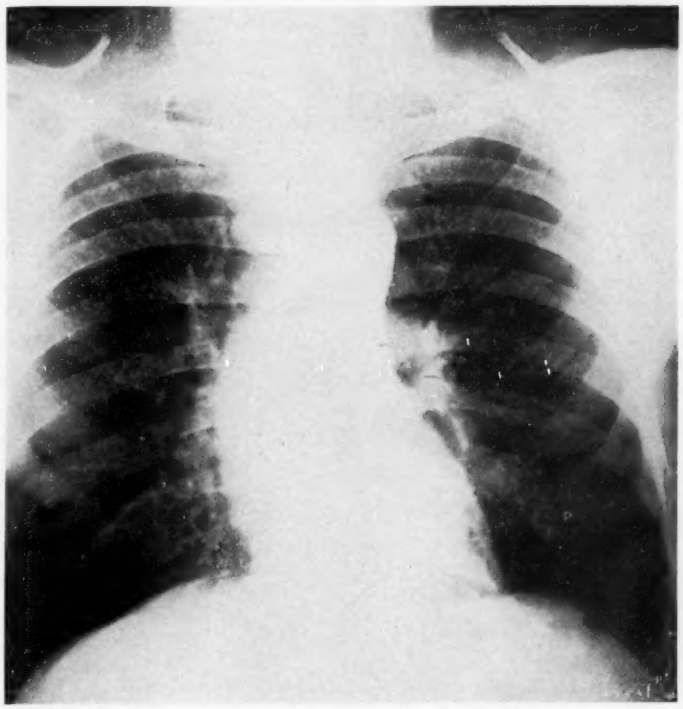
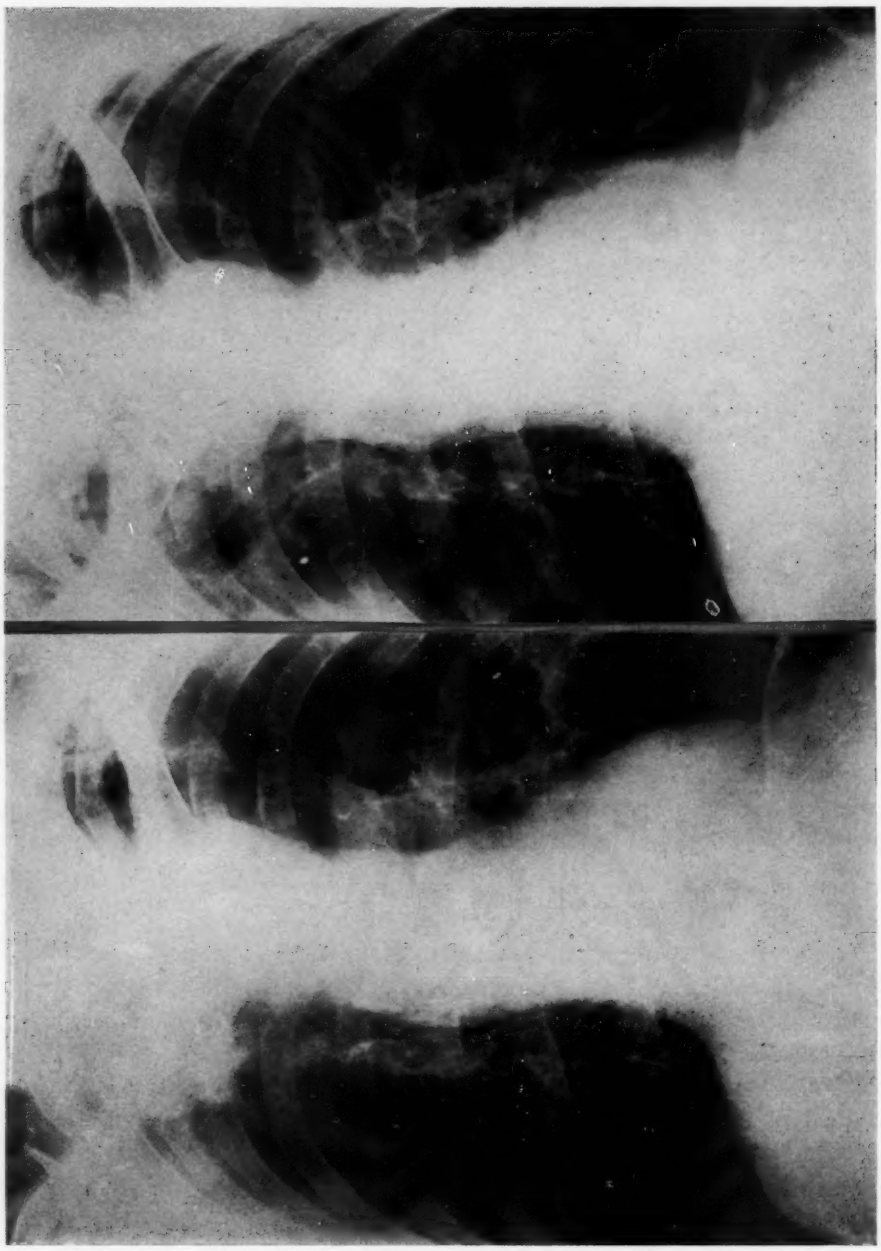


Fig. 2.—X-ray of chest of a 56-year-old male with a squamous-cell carcinoma of the left primary bronchus. The increased hilar shadow is characteristic of the lesion in this location with beginning bronchial obstruction, pneumonitis, and atelectasis.

elevation of the pressure within the tracheobronchial tree. Whether this is on the basis of side-to-side movement of the mediastinum with its deleterious effects upon the normal insufflation of the opposite lung, or whether it interferes materially with the return flow of blood to the heart and consequently diminution of the cardiac output is not definitely understood. However, both of these functions are probably altered. It is well known that a correction of these deleterious effects, aggravated by coughing, can be quickly and easily brought about by the administration of oxygen under a low positive pressure.

That the collapse of the lung which occurs during an exploratory thoracotomy is not in itself especially harmful, and does not reduce the normal lung capacity to a lethal level, has been repeatedly demonstrated. Both animals and human beings may well tolerate reduction in lung function to a marked degree; namely, one-third to one-sixth of their original capacity.[17] This fact is borne out by the frequent observation made during exploratory thoracotomy that the mobile mediastinum sinks well over the midline toward the unoperated side, thus impinging materially upon the function of the presumably normal lung. Fraenckner



*B.*

*A.*

Fig. 3.—X-rays of the chest of a 53-year-old man taken before (*A*) and after (*B*) a one-year period. The patient was treated for tuberculosis for over one year until marked excavation of the tumor occurred. Rib resection and biopsy proved it to be a squamous-cell carcinoma of the lung.

and Bjorkman,[18] on examining the pulmonary ventilation of each lung independently using a method devised by Jacobaeus called bronchospirometry, found that the respiratory function of the lung on the lower side of an unopened chest with a patient in a lateral position was greater than that of the upper side. This was thought to be due to an increased blood supply of the lower lung by gravitation. Although the experimental evidence appears irrefutable, the explanation for the results is not entirely convincing.

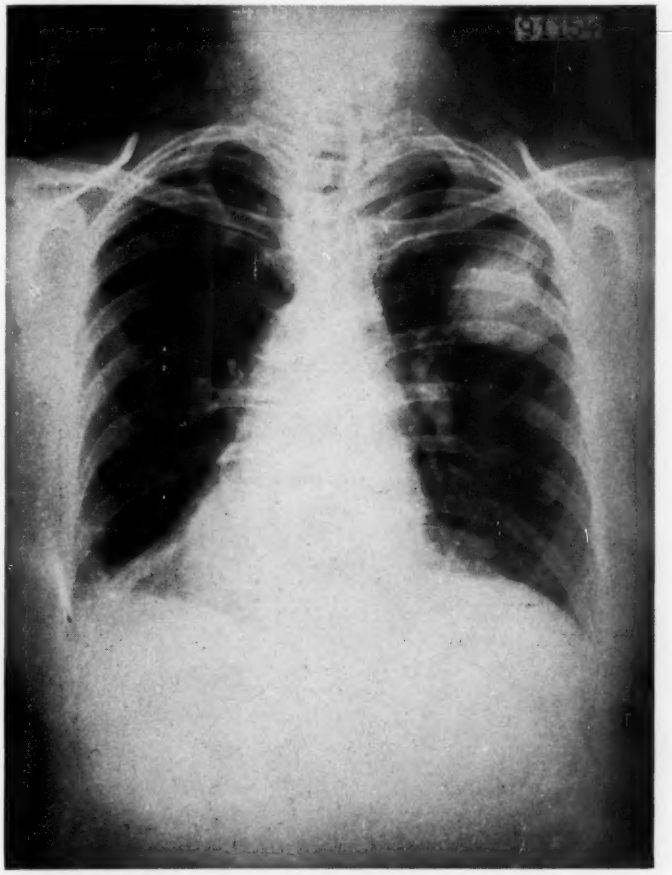


Fig. 4A.—X-ray of the chest of a 62-year-old woman who complained of a nonproductive cough of several months' duration. The right upper and middle lung lobes were resected followed by an uneventful convalescence.

Thus, in view of the many and varied difficulties and confusing ideas regarding this problem during even recent years, a very valid reason is obvious for the delay in making intrathoracic exploration a relatively safe procedure. The application of some of the principles developed within recent years will be discussed further under the heading of anesthesia.

## RESECTION OF LUNG TISSUE

The slow development of a suitable technique for lobectomy and pneumonectomy for clinical usage was not due to a lack of interest in this

subject. The first total pneumonectomy was performed by Rolandus[19] in 1492. In 1881 Gluck[20] removed the entire lung on one side from six dogs and eight rabbits, of which two of the latter survived. Friedrich[21] in 1908, by use of the principle of dissection and separate ligation of vessels, was able to secure a favorable mortality rate in animals. Subsequently, with improvements in surgical technique, pneumonectomy in dogs has been carried out with less than 10 per cent mortality.[22]

*B.*

Fig. 4 *B* and *C*.—*B*. Microscopic section through entire tumor mass which consisted of a thick-walled cavity filled with pus. Guinea pigs injected with the contents of the cavity died of tuberculosis. Diagnosis: tuberculoma of the lung. *C*. Photomicrograph (×120) of wall of cavity seen in *B*. Note lining of cavity by squamous epithelium (this was not continuous throughout) and lymphocytic infiltration of wall. Giant cells were found in some areas.

Lobectomy for tumor and for bronchiectasis was accomplished as early as 1907 by Gluck whose results were later improved by Sauerbruch. Although the first pneumonectomy in animals was performed as early as 1492, the first successful pneumonectomy in man for tumor was not performed until 1933, almost four and one-half centuries later, by

Graham.[23] This has been explained in part as due to the lack of inherent healing in the bronchial wall by Bettman,[24] whose experiments were substantiated by others.[25] It was partly for this reason that mass ligation of the hilar structures was discarded in favor of the dissection technique. This consisted of individual ligation of the vessels and suturing of the bronchus followed by covering of the same with mediastinal pleura to encourage primary healing of the bronchial stump. More recently, compensatory changes following the reduction in lung function have been studied experimentally,[26, 27, 28] the results of which will be discussed under a separate heading.

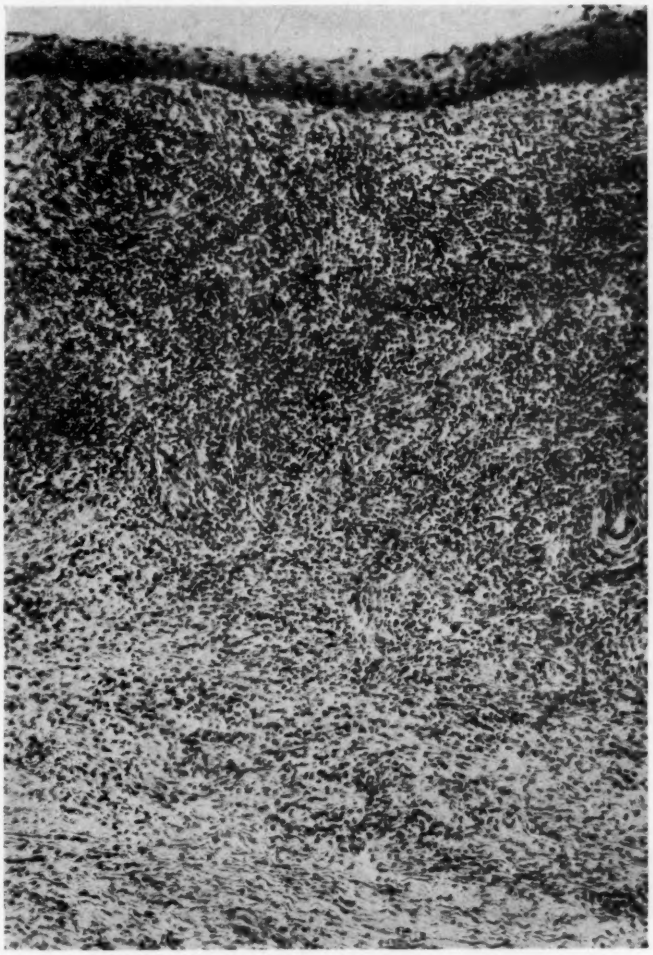
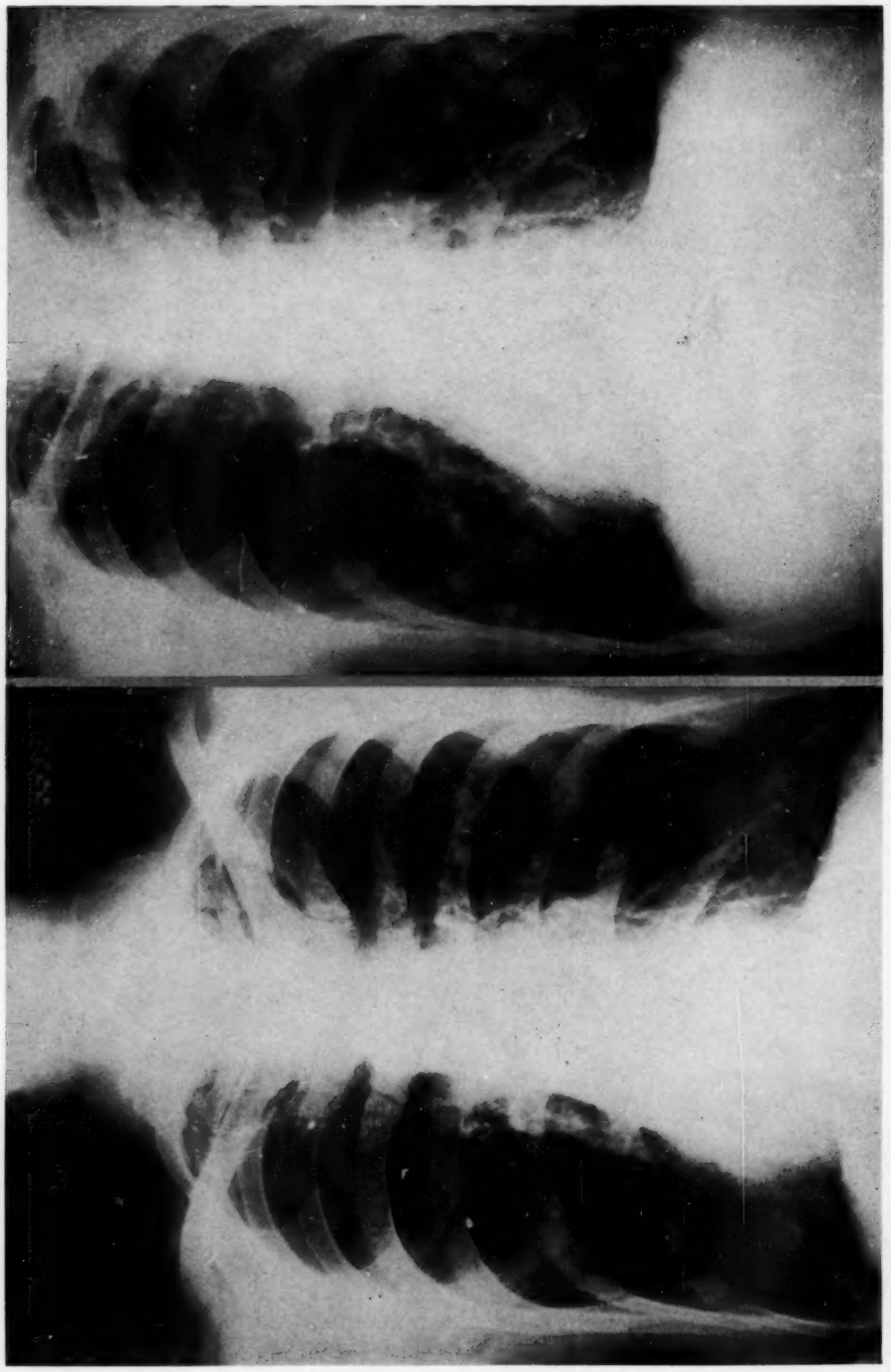


Fig. 4*C*.—See opposite page for legend.

## METHODS OF DIAGNOSIS

The third major factor in the delayed surgical treatment of primary lung tumors was the lack of diagnostic methods. With the discovery of x-ray by Roentgen[29] in 1895 and the subsequent development of an opaque medium, diagnosis of these tumors was much enhanced. The first successful use of the bronchoscope for removing foreign bodies from the

air passages made by Killian[30] in 1897 was another great step forward not only in the establishment of a correct diagnosis during an earlier stage of the tumor but also in the realization of its frequent occurrence. Whereas primary malignant tumor of the lung was once thought to be infrequent and of interest chiefly to the pathologist, with improvement



*B.*

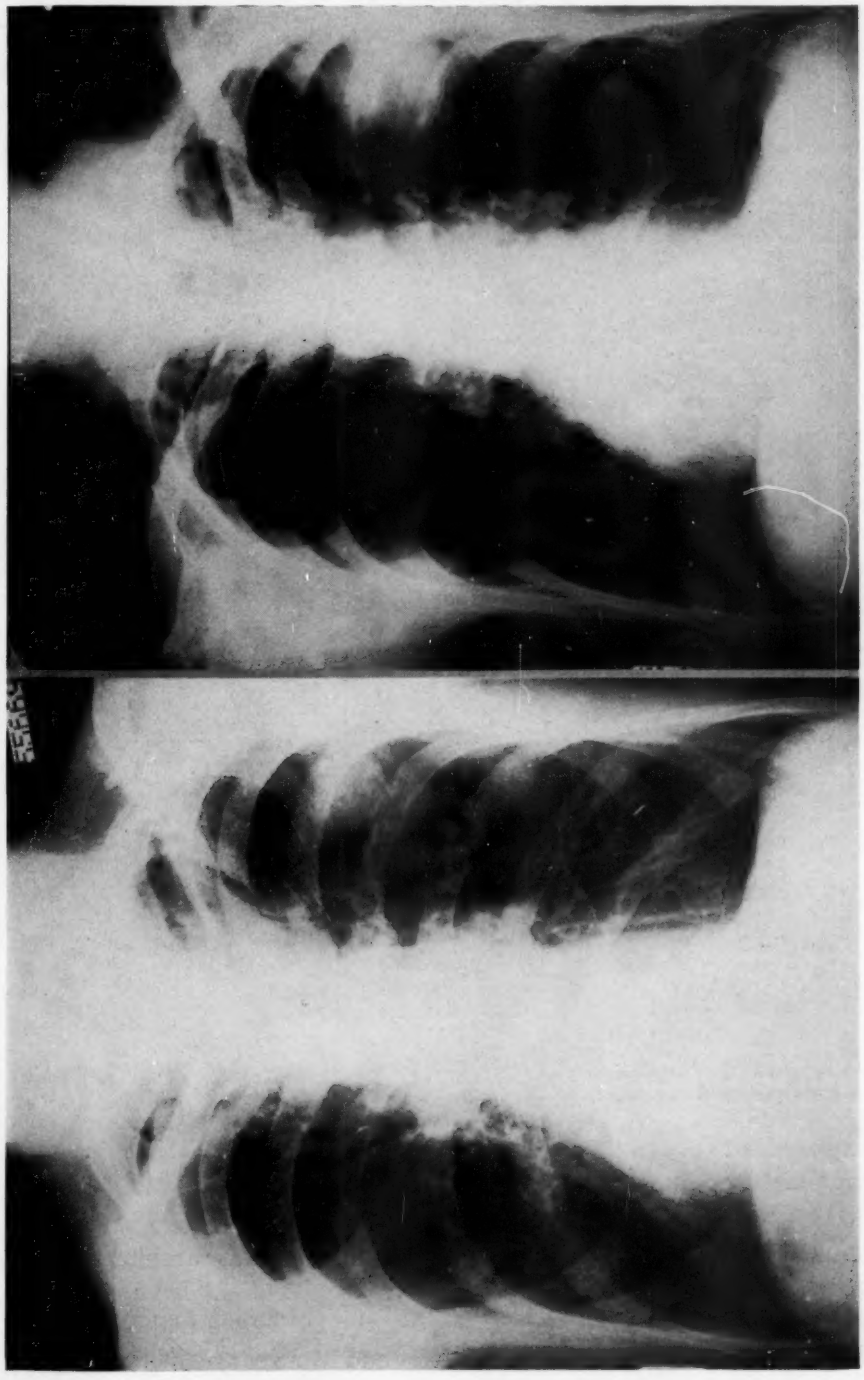
*A.*

Fig. 54-*D*.—Four x-rays of the chest of a 57-year-old male taken on the respective dates: April 5, 1937; Aug. 1, 1938; Dec. 11, 1939; and April 10, 1941; thus over a period of four years. The patient was first seen because of asthmatic wheezing. He was entirely asymptomatic when the last x-ray was taken. Note gradually enlarging opacity in second right interspace anteriorly.

in methods of diagnosis it has been found to rank second in frequency only to carcinoma of the stomach.[31] Thus, it is now appreciated as one of the major problems in the treatment of neoplastic disease.

## CLASSIFICATION OF TUMORS

A discussion of the recent advances in the surgical treatment of primary lung tumor would be incomplete without some attention being



*C.* *D.*

Figs. 5*C* and *D*.—See opposite page for legend.

was entirely asymptomatic when the last x-ray was taken. Note gradually enlarging opacity in second right interspace anteriorly.

given to the variety of tumors involved. For all practical purposes, primary malignant tumor of the lung is synonymous with bronchogenic carcinoma. Other tumors such as sarcoma, endothelioma, etc., can be dismissed as being rare since the variation in cell type and pattern of arrangement in bronchogenic carcinoma has been recognized. As stated above, during recent years the incidence of this tumor has been shown

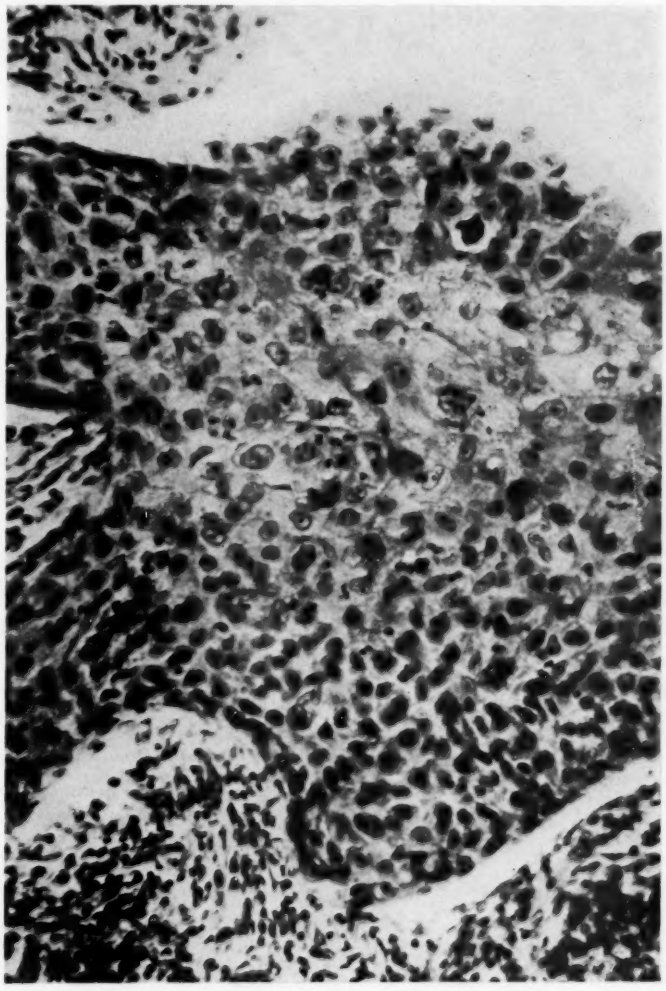
*E.*

Fig. 5 *E* and *F*.—Microscopic section (*E*) and photomicrograph (×325) (*F*) showing a squamous-cell carcinoma of the lung.

to rank second only to that of carcinoma of the stomach. This represents approximately 10 per cent of all malignant tumors. (Seyforth,[32] Jaffé,[33] Koletsky,[34] Simons,[35] Overholt.[36])

A universally accepted classification of bronchogenic carcinoma is not in existence at the present time. Various classifications have been presented from time to time and more recently by Tuttle and Womack,[37] Halpert,[38] Rabinovitch and associates,[39] and Gebauer.[40] The disagree-

ment which persists between various authors in this regard is probably best explained by the marked variation in both the rate of growth and the cell type and arrangement in different tumors. If one is to take evidence of infiltration of surrounding structures, as well as metastases to neighboring lymph nodes and distal tissues and organs as a criterion of malignancy, the length of the clinical course may vary from one to fifteen or twenty years. Naturally this variation in clinical course and histologic appearance has had considerable influence on previous methods of treatment prescribed.



*F.*

Fig. 5*F*.—See opposite page for legend.

Again, the location of the tumor may vary from a main stem bronchus to the extreme periphery of the lung, whether it be a squamous-cell or some other cell type of carcinoma. The location of the tumor is likely to have a definite bearing not only on the clinical course but on the stage at which a correct diagnosis is made. In general, symptoms are manifested earlier in tumors located in the primary stem bronchi, due to irri-

tation of the mucosa and to the development of infection subsequent to obstruction of the air passages. This centrally located group represents about 75 per cent of all bronchogenic carcinomas and has been thought to be the most favorable group for surgical treatment inasmuch as an earlier diagnosis can be established from bronchoscopic examination and biopsy. Indeed, tumors located near the periphery may become several centimeters in diameter only to be found accidentally on x-ray examination before any symptoms have been noted. Again, tumors may become quite large, the center may become necrotic with cavity formation giving rise to the symptoms and signs of lung abscess as the first evidence of the presence of a tumor. In a recent report by Hauser and Wolpaw[41] this course represented about 12 per cent of all bronchogenic carcinomas. Still another group of tumors arising in the main stem bronchi and projecting both into the bronchial lumen and infiltrating the peribronchial structures gives rise to repeated attacks which are diagnosed as pneumonia, the attacks usually extending over a period of several years.[42] This group of tumors has been called benign bronchial adenoma as well as numerous other names, but from the standpoint of cellular structure the benign cannot be differentiated from the malignant variety. Churchill[43] states that this group represents about 5 per cent of all bronchogenic carcinomas.

Purely benign tumors of the lung are relatively rare and include chondroma, lipoma, fibroma, and angioma. These tumors need little consideration since they represent such a small minority of primary lung tumors. Another relatively nonmalignant tumor is the endothelioma, four of which were recently reported by Edwards and Taylor.[44] These tumors, along with the above-mentioned benign tumors, produce symptoms either by pressure upon adjacent structures or by secondary infection of the bronchial tree due to obstruction. An angioma of the lung treated by Tuffier[45] in 1889 involved the chest wall, eroding the ribs by pressure. A number of angiomas have been removed by Sauerbruch.[46] One characteristic of thoracic angiomas, as is common with angiomas elsewhere, is the marked hemorrhage which usually occurs with their removal. This may be serious and is usually controlled by suture and packing.

Primary carcinoma of the lung has received various classifications, the following of which have been most recent: Halpert[38] has divided them into three types, depending upon the embryological direction of growth: (1) the "reserve-cell" carcinoma, (2) cylindrical-cell carcinoma, and (3) squamous-cell carcinoma. He believes that all tumors arise from one cell; namely, the basal cell. Ochsner and DeBakey[47] find this to be the most logical classification of primary carcinoma of the lung. Gebauer[40] divides bronchogenic carcinoma into three fundamental types; namely, small-cell carcinoma, adenocarcinoma, and squamous-cell carcinoma. He believes that this tumor "cannot be regarded pathologically or clinically as a single entity." A third classification is that

given by Rabinovitch, Hochberg, and Lederer.[39] These authors classify bronchogenic carcinoma into three main groups as follows:

1. Squamous-cell carcinoma
2. Cylindric-cell carcinoma which includes
   a. Adenoma
   b. Undifferentiated cell carcinoma, including
      (1) Medullary
      (2) Round cell
      (3) Oat cell
3. Pleomorphic-cell carcinoma

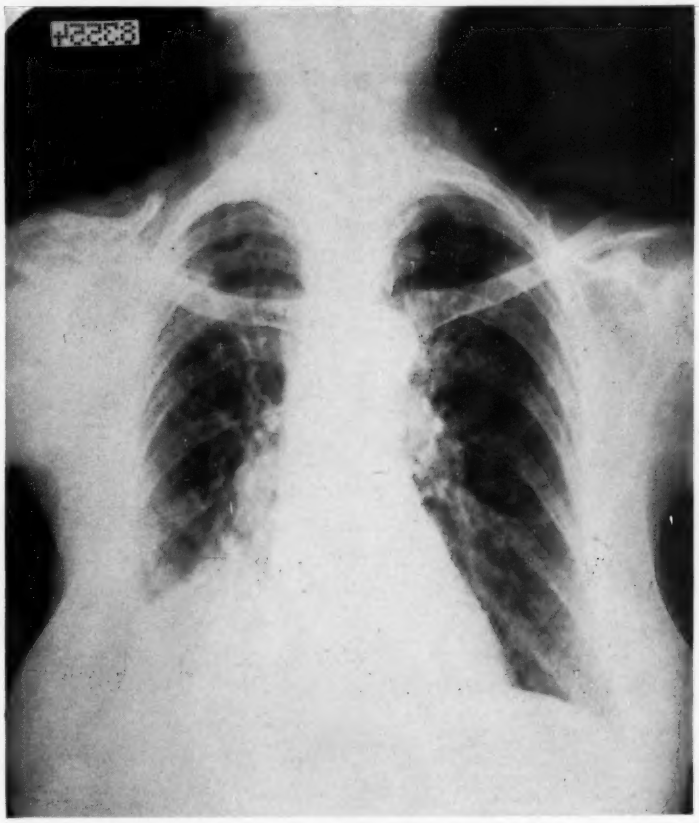


Fig. 6A.—X-ray of chest of a 62-year-old woman who complained of a productive cough, repeated hemoptyses, and attacks of pneumonia over a period of several years' duration. Note triangular-shaped opacity in lower right lung field due to atelectasis and pneumonitis.*

They state that the unicellular theory seems to hold true and explains the various forms of malignant growth that may arise in the bronchial tree. A fourth classification has been presented by Tuttle and Womack in collaboration with Graham[37] which divides all tumors into two groups; i.e., squamous-cell carcinoma and mixed tumors of the lung. These authors have presented evidence that various cell types and arrangement of the same may be found within the same tumor and that many apparently benign tumors are actually malignant, as demonstrated by metastases in the lymphatics and by invasion of adjacent structures.

Thus it is quite apparent that a uniform opinion regarding the pathologic characteristics of bronchogenic carcinoma does not exist at the present time. This, in the past and to some extent also at the present, has added greatly to the confusion regarding the early diagnosis and proper therapy for these tumors. It is quite probable that the unicellular theory is correct and that the rate of growth and degree of malignancy is variable regardless of the type of cells or their arrangement. What is more important is that these tumors are all potentially malignant and should be treated as such, following the principles for treatment of carcinoma elsewhere in the body; namely, the complete removal of all of the tumor-bearing tissue. When considered from this aspect an earlier diagnosis may be expected, and proper therapeutic measures may be instituted at a time when the tumor is still in the operable stage.

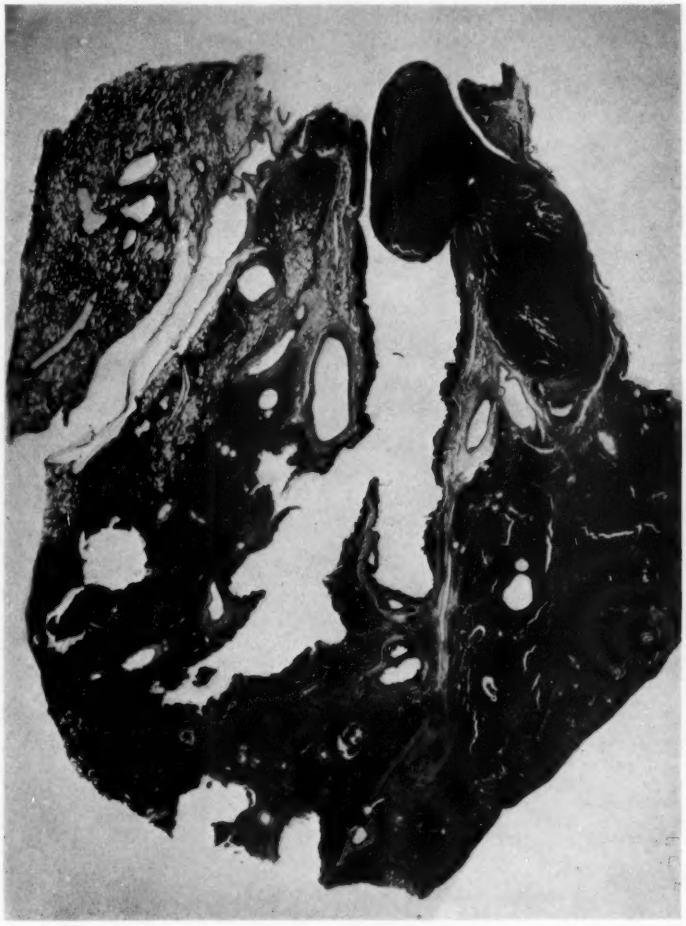
*B.*

Fig. 6 *B* and *C*.—Photograph of resected right lower lobe (*B*) and microscopic section (*C*) through entire specimen. Note bronchial tumor filling a secondary bronchus and extending out into the primary bronchus of the lobe. The completely obstructed portion of the lung is atelectatic, the incompletely obstructed portion is bronchiectatic.*

## DIAGNOSIS

The clinical symptoms and physical findings in bronchogenic carcinoma are extremely variable, not only in different patients but at different periods in the same patient. Statistics covering this feature should not be gathered from all tumors as one group, nor from all stages of the tumor, for this would be very misleading. In general, one can say that a large proportion of the symptoms are on the basis of infection of the respiratory passages due to varying degrees of obstruction by the

tumor. To a lesser extent symptoms are produced by direct invasion of adjacent structures. On the other hand, many tumors located in the peripheral portion of the lung remain quiescent for months or even years, regardless of the type of tumor cell or their arrangement (Fig. 5). Again, as mentioned above, central necrosis with cavity formation and infection in some tumors produces symptoms and signs of pulmonary suppuration, tuberculous or nontuberculous in nature. Most of these features have been discussed by others[41, 48] and need not be given detailed discussion here. It will be apparent at once that the sooner symptoms



*C.*

Fig. 6*C*.—See opposite page for legend.

are produced by a tumor, the greater the likelihood that an early diagnosis will be made, providing diagnostic methods are properly used. Thus, tumors which remain "silent" and are found only late in the course of the disease will have a much poorer prognosis, providing their degree of malignancy is the same.

One of the principal factors in diagnosis is suspicion of the presence of tumor in all patients over 40 years of age having symptoms referable to the chest. When the high incidence of the tumor is kept in mind,

a search will be rewarded by a higher percentage of early diagnoses. If fluoroscopic examinations were made as a routine at regular intervals on all patients in this group, a higher percentage of the peripheral lung tumors would be diagnosed at an earlier stage thus improving the prognosis for the group. For the centrally located variety, bronchoscopic examination and biopsy of the tumor in all patients with unexplained cough would give rise to an early diagnosis, even before x-ray evidence is demonstrable.

Other diagnostic methods which are available include examination of the sputum as described by Dudgeon[49] for malignant cells which give a positive finding in a high percentage of patients where tumor cells are present in the sputum. This is especially applicable to tumors located peripherally with necrosis of the central portion. There is also available examination of pleural effusions by Mandelbaum's method[50] which

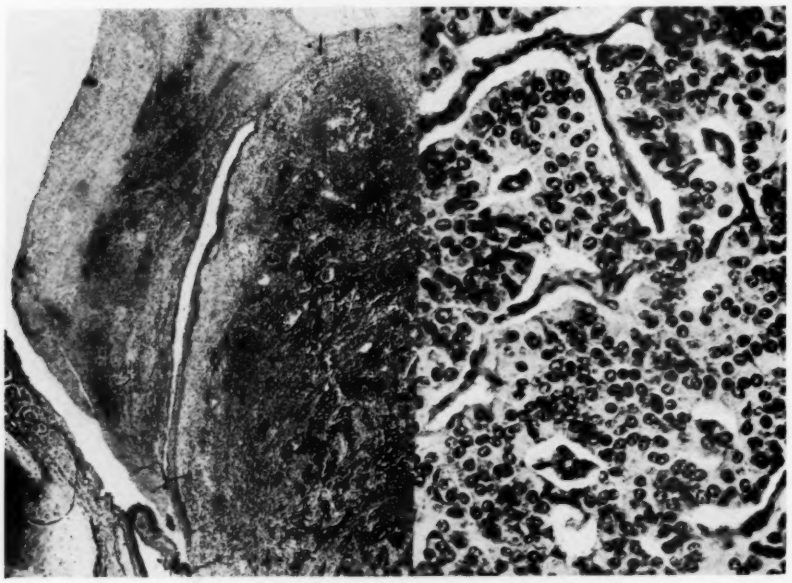


Fig. 6*D.*—*Left.* Photomicrograph (×27) showing intrabronchial tumor with its surface layer of fibrous tissue covered by stratified squamous epithelium and at the upper left a layer of fibrin infiltrated by leucocytes. *Right.* Photomicrograph (×560) showing the character of the tumor cells and their stroma.*

includes centrifugation and fixation of the sediment with subsequent staining for microscopic examination. Both of these diagnostic methods are usually positive only after the tumor has progressed beyond the operative stage. A third diagnostic procedure which has been reported of value by some authors is aspiration biopsy. Here again, its application is only in peripherally located tumors and is likely to be made after the tumor has become inoperable. The advisability of its employment is questionable since spread of the tumor along the path of the needle puncture has been frequently observed. Since bronchoscopic examination with biopsy of tumor tissue is applicable to about 75 per cent of all primary carcinoma, it remains the most valuable procedure for improving surgical treatment.

*Differential Diagnosis.*—One of the most difficult conditions to be differentiated from peripherally located carcinoma is pulmonary tuberculosis. As already pointed out by Hauser and Wolpaw, cavitation occurs in about 12 per cent of the tumors and both roentgenologically and clinically may simulate the appearance of pulmonary tuberculosis (Fig. 3). Again, one may occasionally see a solitary tuberculous lesion which produces an opaque shadow on x-ray examination and which appears not unlike a peripherally located primary lung tumor (Fig. 4). In the later stages of the tumor, empyema and nontuberculous lung abscesses are often presented as the primary diagnosis. Again, in the more benign, centrally located tumors due to the presence of infection of the air passages, bronchiectasis and repeated attacks of pneumonia are commonly mistaken as the primary diagnosis. Thus it is evident that when these lesions occur in patients where primary carcinoma is likely to be found an early differentiation can be made only by observation and by the use of available diagnostic methods.[51, 52]

*(To be concluded in the December issue. The references will accompany the last section.)*

# Review of Recent Meetings

## REPORT OF THE MEETING OF THE AMERICAN ASSOCIATION OF GENITO-URINARY SURGEONS, HOT SPRINGS, VA.

MAY 29-31, 1941

C. D. CREEVY, M.D., MINNEAPOLIS, MINN.

*(From the Department of Urology, University of Minnesota Medical School)*

THE FIFTY-THIRD annual meeting of the American Association of Genito-Urinary Surgeons was held in Hot Springs, Va., May 29, 30, and 31. The meeting opened on May 29 with the following papers:

**W. J. Engel**, Cleveland, reported two cases of pheochromocytoma of the adrenal. In each there was a variable but not paroxysmal hypertension, with symptoms suggesting hyperthyroidism. One patient had a severe diabetes and died from an infection, the tumor being discovered at necropsy. The second patient, a 19-year-old girl, had attacks characterized by a feeling of intense heat, followed by faintness and perspiration. Pyelography and perirenal air insufflation were not diagnostic; the tumor was discovered at exploration; recovery followed its removal. The importance of adrenalin and transfusion during and immediately after operation was stressed.

**B. H. Hager**, Los Angeles, added to the meager literature another example of an apparently solitary metastasis from a renal neoplasm. A tumor of the left chest wall of eight years' standing proved, on excision, to be a renal carcinoma. Pyelography incriminated the left kidney which was removed a month later. Twenty-five months after operation the patient was well.

**G. S. Foulds**, Toronto, Ontario, described a neoplasm of the kidney which in some areas was a papillary cystadenocarcinoma, in others a hypernephroma, and in still others intermediate between the two.

**H. G. Bugbee**, New York City, presented a case of renal tuberculosis in which the pyelogram was that of a papillary neoplasm of the renal pelvis. This was due to a tuberculoma.

**W. C. Quinby**, Boston, discussed current theories which attribute some hypertension to local renal disease, and reported experiments in which a temporary rise of systemic blood pressure followed temporary occlusion of the renal artery in animals with vagi cut, heart denervated, and adrenals removed. This he regarded as proof that the mechanism of hypertension is "humoral."

**V. J. O'Conor**, Chicago, reported two very interesting examples of hypertension in young men, each with a solitary kidney, hydronephrosis, and ureterocele. In both,

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the blood pressure returned to normal and had remained so for two and fifteen years, respectively, after cystoscopic destruction of the ureterocele.

**W. H. Toulson,** Baltimore, reviewed 41 perinephric abscesses, of which 13 were secondary to renal suppuration, 27 were apparently primary, and 1 was an extension of inflammation from an adjoining viscus.

**G. C. Prather,** Boston, studied 72 cases of pyelonephritis of pregnancy, 40 per cent of which recurred in subsequent pregnancies. He could not detect any increased tendency to hypertension in subsequent pregnancies; i.e., a patient who has had a pyelonephritis is no more likely to have hypertension than one who has not.

**J. K. Ormond,** Detroit, lavaged the renal pelvis with 2.5 per cent silver nitrate for an acute pyelonephritis. Nine years later nephrectomy was done for a pyonephrosis with an impassable ureteral stricture, and deposits of silver were demonstrable in the interstitial tissue. Destruction was attributed to extravasation of the silver nitrate into the parenchyma.

**D. M. Davis,** Philadelphia, presented a cystoscopic table with a top and legholders which could be slid up away from the Bucky diaphragm and over a fluoroscopic apparatus, without disturbing the patient.

The following papers were presented on May 30:

**A. J. Scholl,** Los Angeles, reviewed 6 cases of gunshot wounds of the kidney seen in ten years, and concluded that the injury of the kidney was usually secondary in importance to that of the intestines, wounding of which often led to death.

**A. L. Dean, Jr.,** New York City, declared that no satisfactory routine for the treatment of Wilm's tumors of the kidney has been established. The tumors are capricious in their response to irradiation, after which they always recur. Irradiation followed by nephrectomy is the most satisfactory treatment thus far available, 2 of his patients so treated being well for four and one-half years.

**G. W. Fish** and **G. F. Cahill,** New York City, had records of 58 cases of polycystic kidneys. Twenty-three came to operation (drainage of cysts, abscesses, nephrectomy for complicating tumors, etc.), of which 17 were living and apparently well for from one to sixteen years.

**G. G. Smith,** Boston, discussed the indications for ureteroenterostomy, basing his conclusions on 54 patients. The surgical mortality should be below 15 per cent. Late complications are rather frequent, and the utility of the operation in cancer of the bladder is still debatable. He employs unilateral extraperitoneal transplantation without catheters.

**F. H. Colby,** Boston, advocates cutaneous ureterostomy in tuberculosis involving both kidneys or a solitary kidney in the presence of intolerable cystitis. If a satisfactory projection of ureter beyond skin can be arranged, catheters can be omitted and modified colostomy cups used. In 10 cases gratifying relief was secured.

**C. D. Creevy,** Minneapolis, described 4 unusual examples of obstruction at the ureteropelvic junction including 1 granuloma, 3 polyps, and 1 recurrent obstruction above the ureteropelvic junction by accessory vessels deliberately left at operation. He concluded that the junction should always be explored during plastic operations, and that accessory vessels should always be divided.

**Alexander Randall,** Philadelphia, reported a tumor of the ureter which was diagnosed by urography and treated by nephroureterectomy, but which proved to be an endometrioma on section.

**W. J. Baker,** Chicago, resected a vesical neoplasm which proved to be an endometriosis.

**M. L. Boyd,** Atlanta, Ga., discussed an ulcer of the bladder which led to hydronephrosis and refused to respond to protracted conservative treatment. It was resected and found to be inflammatory, presumably from infection with *Streptococcus faecalis.*

**C. F. Rusche,** Hollywood, Calif., reviewed two vesical neoplasms which on removal were seen to consist of deposits of amyloid in areas of chronic inflammation. Such solitary deposits have been found in other organs but cannot be explained satisfactorily.

**Leon Herman,** Philadelphia, discussed several unusual urological cases, chief among which were a scrotal metastasis from a carcinoma of the stomach and a testicular metastasis from a carcinoma of the bladder.

On May 31, the following papers were presented:

**H. C. Bumpus, Jr.,** Pasadena, Calif., discussed the treatment of carcinoma of the prostate and concluded that transurethral resection of obstructing tissue gives the patient more comfort than any other single method. Symptomless carcinomas are best let alone; the radical operation, because of its limited applicability, the likelihood of distant metastases from a small primary, its high mortality, and difficulties in accurate microscopic diagnosis, offers no advantages.

**W. P. Herbst, Jr.,** Washington, D. C., recounted his experience with estrogens in the treatment of prostatic carcinoma. Seven patients were treated, all with apparent benefit, especially in the relief of pain from metastases. Whether the benefit results from depression of the anterior pituitary or of the testes is not known.

**C. M. Johnson** and **Frank Hinman,** San Francisco, and **J. M. Carr,** Stockton, Calif., have abandoned the so-called radical orchidectomy because crossed lymphatic metastases defeat its purpose so frequently. Since 1936, they have subjected 44 testicular neoplasms to simple orchidectomy followed by irradiation. All patients who had increased urinary prolans are dead, the longest survival being fifteen months. Twenty-three of 30 with normal prolans are living fifteen to seventy-two months. The Friedman (rabbit) test for prolans is too insensitive to be of value in testicular neoplasms.

**R. C. Graves,** Boston, and **K. B. Lawrence,** Wrentham, Mass., resorted to castration and irradiation of a patient with bilateral testicular neoplasms and palpable abdominal metastases. Although the masses disappeared, the patient died in a few months.

**N. J. Heckel,** Chicago, observed that alpha-estradiol (progynon) administered to patients with benign prostatic hypertrophy caused enlargement of the breasts, degeneration of the testes (aspiration biopsy), disappearance of the seminal fluid, aspermia and impotence, but did not affect the size of the prostate nor its symptoms.

**B. S. Barringer,** New York City, called attention to the value of the subarachnoid injection of absolute alcohol in controlling the pain of apparently hopeless cancer. In 3 instances, the disappearance of pain turned the tide in the patient's favor, and the tumor was then controlled by irradiation with seeming restoration of normal health.

**R. M. Nesbit** and **R. H. Cummings,** Ann Arbor, Mich., found that the routine use of prostigmine in patients with postoperative urinary retention was ineffective. Given prophylactically, it apparently did prevent retention in a small percentage of cases.

**H. G. Hamer,** Indianapolis, presented the case of an unusual prostatic abscess, which was small, centrally located, and which was mistaken for a benign hypertrophy by several examiners. The patient died of cardiac failure and pneumonia, and the abscess was found at necropsy. It had not been influenced by sulfanilamide.

**W. N. Wishard, Jr.,** Indianapolis, reviewed the subject of carcinoma of the male urethra, 171 of which are reported in the literature, 20 since 1938. He concludes that its frequency is increasing. His patient had a transitional cell carcinoma of the penile urethra near the external meatus, five years after fulguration had cured a papilloma of the membranous urethra. Radon and x-ray apparently destroyed the tumor, the patient now being well (except for a stricture) for two years.

# Book Reviews

**Body Mechanics in Health and Disease.** By J. E. Goldthwait, L. T. Brown, L. T. Swaim, J. C. Kuhns, and W. J. Kerr. Ed. 3. Pp. 316, with 121 illustrations. Philadelphia, 1941, J. B. Lippincott Co. $5.

This volume is essentially a study of chronic diseases associated with faulty body mechanics. The authors are recognized experts in their fields of orthopedic surgery or internal medicine, but it may be questioned how acceptable some of the statements would be if less well-known writers had published this book. Certain statements are not only illogical but are lacking in proof. For instance, on page 104, could not "rest" alone, and not "the correction of the faulty body mechanics" have helped the heart failure in the patient with chronic valvular disease? On page 108, the description of the type of individual with hypotension is not statistically verified. There is too much armchair thinking in the discussion of anatomy and diseases of the duodenum (page 141) and small intestine. Most of the illustrative cases concerning the effect of posture on certain visceral disturbances impressed the reviewer as being incomplete and inconclusive.

Throughout the book, too much emphasis is placed on the role of body mechanics in the treatment of disease. May not faulty body mechanics be more often the result rather than the cause of certain physical disorders?

Some considerations concerning corrective and preventative treatment of faulty posture are given. An extensive bibliography and a workable index are appended. The binding and printing of the book are excellent.

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**Training and Efficiency: An Experiment in Physical and Economic Rehabilitation.** By E. Jokl, E. H. Cluver, C. Goedvolk, and T. W. DeJongh. Pp. 188. Johannesburg, South Africa, 1941, The South African Institute for Medical Research.

On the flyleaf of this book there appears a quotation which is not merely the keynote of the present book but which also represents the fundamental orientation of the work of the Johannesburg group. The quotation is from Professor John Ryle's opening address to the students of the Cambridge Medical Faculty on Oct. 15, 1940:

"By one means or another you must develop the social conscience, which has, in the view of many of us, been too little evident in the years preceding the war. Although there have always been noble and notable exceptions in every community it has seemed to me that medical students and doctors as a body, excusing themselves on the grounds of their many preoccupations with the curriculum or the anxieties of practice, have held themselves too much aloof from the larger social problems."

It is logical that the social responsibility of medicine must begin with scientific consideration of the physiology and anatomy of the individual. The obvious second step is to inquire into the influence of mode of life and environment on the individual as a functional machine and as a citizen. Such questions have been the subject of innumerable treatises "about it and about," but usually eloquent verbiage and argument have had to suffice in place of concrete material fact. The present

work supplies some concrete facts about the effects of six months' physical training on raw recruits in the South African Army.

The results reported on the thirty-two young men are of great interest and their implications are of first rate importance. The alterations in posture and physiognomy are striking. Together with the changes recorded in the performance tests, they provide a powerful argument for physical training for all young men. The authors exhibit justifiable gratification at the amount of work they accomplished in this study, but they should be the first to agree that they have only pointed the way to much more exhaustive studies. They have not touched the question of "efficiency" in the physical or chemical sense and the whole field of metabolic alterations is left blank. Such practical matters as the kind of physical training regime best suited to promote the desirable alterations are not mentioned. Recognition of the limitations of the present work is not to detract from its virtues but simply to indicate that the social importance of such problems merits the efforts of dozens of other groups.

The book itself is a curious mixture of appeal to popular understanding and of scientific data presented in rather tedious garb. Careful reading, or rather study, is necessary to keep track of the relative changes in the numerous subgroupings of the men: "best performers," "poorest improvers," etc. The presentation of all data in extenso detracts from the text though the flagging interest of the reader is revived from time to time by amusing pencil drawings depicting the conversion of the puny and aimless loafer to the stalwart young man who is an asset to himself and his community. The references are not numerous but cover a fair sample of recent material of relevancy. We can commend the work to the thoughtful consideration of physicians, educators, and government administrators alike and hope that Jokl, Cluver, and their colleagues will continue their valuable studies in this field.

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**Sulfanilamide and Related Compounds in General Practice.** By Wesley W. Spink. Ed. 1. Pp. 256. Chicago, 1941, Year-Book Publishers, Inc. $3.

This volume concerning sulfonamide therapy is the best published to date. The first chapter gives a short historical review; the subsequent chapters deal with the indications and results of treatment with the different sulfonamide compounds. The author writes from a wide clinical experience; his evaluations are sound, his enthusiasm temperate, and his review of the pertinent literature critical and concise. An extensive bibliography and a workable index are appended. Every doctor who wishes to have the latest knowledge concerning sulfonamide therapy should read this book.

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**The Treatment of Cancer and Allied Diseases** (3 volumes). By George T. Pack and Edward M. Livingston. Ed. 1. Pp. 2598, with 1,500 illustrations. New York, 1941, Paul B. Hoeber, Inc. $36.

Without question, these are the best composite group of volumes published on the management of malignancy to date. A number of years ago Zweifel and Payr edited a similar three volume work on the malignancy problem. However, the present work written by 147 authors, largely American, under the editorial supervision of Pack and Livingston, is a far superior collection of monographs, from the standpoint of the clinician. Written by leaders in their respective fields, these books, covering systematically the treatment of all body malignancies, present the best accomplish-

ments in the cancer problem. The surgical, as well as the irradiation aspects of treatment, are presented. A unique feature of the volumes, new to this reviewer, is a repelative discussion of technical procedures by authors, employing somewhat dissimilar approaches to the same problem. For instance, in Volume II, the reader, interested in informing himself on the best current opinion on the surgical treatment of cancer of the rectum, will find chapters written by such men as Jones, Rankin, Lahey, Babcock and others, each detailing the features of his particular operation.

These volumes constitute a real addition to the literature of the treatment of malignancy and will be found eminently useful and practical by radiologists and surgeons alike.

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**Field Surgery in Total War.** By Douglas W. Jolly. Ed. 1. Pp. 242, with 32 illustrations. New York, 1941, Paul B. Hoeber, Inc. $3.50.

The special feature of this book, which particularly recommends it, is that it is written by a surgeon just fresh from an active surgical service in war; viz., the recent Spanish Revolution. The first section of the book deals with organization and tactical disposition of surgical units in the field. The author is an ardent supporter of the "three point forward system." This scheme embraces a casualty classification post for the proper division of cases; a No. 1 Hospital for the most urgent cases, and a No. 2 Hospital for the less urgent cases with sector evacuation and Base Hospitals in the rear.

The subject matter of surgical treatment of war wounds of the various parts of the body is treated in an orthodox fashion. The chief weakness of the book lies in the failure to mention or discuss the types of injury inflicted by the various implements of war. Certainly such a discussion might reasonably be expected to be found in such a text. Similarly, additional illustrations would augment the value of the text. Within the space of 240 pages, the author has succeeded in compressing a large broad personal experience with war wounds. It is a worth-while manual for surgeons, interested in the casualties of war, to study.